Master Thesis

European Master of Health Economics and Management

Development of a microsimulation model to evaluate the cost-effectiveness of screening and lifestyle intervention for prediabetes

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Date of submission: 01.06.2023

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Abbreviations

2-h PG	two-hour post-challenge glucose
ADA	American Diabetes Association
AEs	Adverse events
BMI	Body mass index
CBA	Cost-benefit analyses
CEA	Cost-effectiveness analysis
CHF	Congestive heart failure
CI	Confidence interval
CVD	Cardiovascular disease
FPG	Fasting plasma glucose
GDRS	German diabetes risk score
HbA1c	Glycated haemoglobin A1c
ICER	Incremental cost-effectiveness ratio
IFG	Impaired fasting glucose levels
IGT	Impaired glucose tolerance
LI	Lifestyle intervention
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
PD	Prediabetes
PD(dHR)	Detected prediabetes with high risk of developing type 2 diabetes

PD(dLR)	Detected prediabetes with low risk of developing type 2 diabetes
PD(ud)	Undetected prediabetes
PLIS	Prediabetes Lifestyle Intervention Study, as described in Fritsche et al. (2021)
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life
RPG	Random plasma glucose
SD	Standard deviation
T2D	Type 2 diabetes
T2D(d)	Detected type 2 diabetes
T2D(ud)	Undetected type 2 diabetes
WHO	World Health Organization
WTP	Willingness-to-pay

Table of contents

Preface

This thesis is part of the completion of the Master programme "European Health Economics and Management (Eu-HEM)". The thesis is written in a research paper format, and it consists of two parts. Part I serves as an extended introduction to the topic and includes detailed information on background of the disease area, type 2 diabetes and prediabetes. This encompasses framing the disease area and epidemiology, as well as screening and prevention strategies. Additionally, part I provides the theoretical framework for the thesis and summarizes existing literature.

Part II, the research paper, entails a manuscript summarizing the methodology, results, and discussion of the thesis. This section is self-containing and may be submitted to journals without the extended introduction (Part I), but possibly including appendices of this thesis.

Part I: Introduction

1. Disease background & epidemiology

Type 2 diabetes mellitus (T2D) is a metabolic disorder characterised by elevated glucose levels caused by gradually worsening pancreatic ß-cell dysfunction and thus insufficient production of insulin, combined with insulin resistance in muscles and organs. This leads to elevated levels of blood glucose, with simultaneously high levels of insulin. However, due to the insulin resistance in the liver, muscles and adipose tissue, the glucose cannot be utilized as a source of energy. Type 1 diabetes differs from T2D in that individuals with type 1 diabetes undergo an autoimmune process leading to the destruction of ß-cells within the pancreas, resulting in a complete absence of endogenous insulin production (Chatterjee et al., 2017; DeFronzo et al., 2015; Leahy, 2005).

Multiple aspects are involved in the development of T2D, including genetic and environmental influences on individuals' health. Risk factors for developing T2D include older age, a family history of T2D, overweight or obesity, smoking, and an unhealthy dietary pattern consuming lots of sugar-sweetened beverage and red meat (Chatterjee et al., 2017; DeFronzo et al., 2015). For a comprehensive discussion of genetic and environmental factors involved in the pathophysiology of T2D, refer to the paper of DeFronzo and colleagues (2015).

Diagnostic criteria to determine whether a patient has T2D are fasting plasma glucose (FPG) levels greater or equal to 126 ml/dL (7.0 mmol/L), glycated haemoglobin A1c (HbA1c) levels greater or equal to 6.5% (48 mmol/mol), or two-hour post-challenge plasma glucose (2-h PG) levels of at least 200 mg/dL (11.1 mmol/L), though exact cut-off values for the diagnosis are sometimes debated and may vary according to country-specific guidelines (American Diabetes Association, 2014; World Health Organization, 2019).

T2D is frequently preceded by prediabetes, which is summarizes a range of characteristics subjecting individuals to particularly high risk of developing T2D. Individuals with prediabetes present with impaired fasting glucose levels (IFG), impaired glucose tolerance (IGT), elevated HbA1c levels or a combination of these aspects. IFG manifests as elevated plasma glucose levels when fasted, which are not yet high enough to qualify as T2D. In contrast to this, IGT is characterised by insulin resistance of the muscles and insufficient insulin secretion after meals. HbA1c levels to qualify as prediabetic are most commonly between 5.7 and 6.4% (39 and 47 mmol/mol) (DeFronzo et al., 2015).

Cut-off values for IGF and HbA1c are somewhat arbitrary and occasionally debated (Gyberg et al., 2015), and therefore there is a fluent transition between the clinical pictures of prediabetes and T2D (American Diabetes Association, 2014; Rodgers et al., 2021). The clinical presentation of patients with prediabetes or T2D may vary considerably, and is also influenced by aspects such as age, comorbidities, and glucose management through lifestyle and medication (American Diabetes Association, 2014; DeFronzo et al., 2015).

It is estimated that between 3 and 18% of individuals with prediabetes progress to T2D annually (DeFronzo et al., 2015; Sallar & Dagogo-Jack, 2020). This progression rate is mainly modulated through HbA1c levels, but blood pressure, liver fat content, blood lipid levels and hypertension also play a role, among other factors (Anderson et al., 2016; Selvin et al., 2010). The risk of progression from normal glucose tolerance to prediabetes, but also from prediabetes to T2D can be significantly lowered through effective blood glucose management and moderate weight loss (Alberti et al., 2007; DeFronzo et al., 2015; Lindström et al., 2006; Uusitupa et al., 2019).

As of 2010, 7.4% of men and 7.0% of women aged 18 to 79 in Germany were diagnosed with T2D. Based on survey data and in combination with lab analyses, it is is estimated that at least an additional 1.2% of women and 2.9% of men have T2D, though many cases remain undetected, especially in early stages of the disease when the clinical presentation is ambiguous (National Diabetes Surveillance at the Robert Koch Institute, 2019; Tamayo et al., 2016). Models predict that the number of patients with diagnosed T2D will double by 2040, placing a considerable strain on the healthcare system (Voeltz et al., 2022). Prevalence of T2D is higher in older age groups and those with lower educational backgrounds in both sexes (National Diabetes Surveillance at the Robert Koch Institute, 2019). Data on the prevalence of prediabetes are scarce due to the lack of a structured screening programme, but it is estimated that one in five Germans have prediabetes as of 2010. Prediabetes is more common in men, with an estimated prevalence of 24.4% (Heidemann et al., 2016). Longitudinal analyses suggest a shift from undiagnosed to diagnosed T2D and a slight decrease of prediabetes incidence rates, but the high prevalence still calls for action to prevent or the delay of the disease (Heidemann et al., 2016).

Diet modifications, increased physical activity, and moderate weight loss have proven to be effective strategies in preventing T2D. A well-balanced diet that is low in saturated fats, refined sugars, and processed foods, while rich in fruits, vegetables, whole grains, and lean proteins, can help maintain a healthy body weight and reduce the risk of diabetes (Sami et al., 2017).

Regular physical activity plays a crucial role by improving insulin sensitivity, lowering blood glucose levels, and promoting weight loss. Engaging in aerobic exercises, such as brisk walking or cycling, as well as strength training, can significantly reduce the risk of developing T2D (Alberti et al., 2007). Furthermore, achieving and maintaining a healthy weight through a combination of healthy eating and regular exercise can further decrease the likelihood of developing this metabolic disorder (Alberti et al., 2007; DeFronzo et al., 2015).

Lifestyle interventions encompass various strategies aimed at T2D by modifying behaviours such as dietary patterns and physical activity. These interventions have demonstrated considerable success in reducing the risk of developing diabetes (Dunkley et al., 2014; Lindström et al., 2006; Tuomilehto et al., 2011). However, it is important to acknowledge the challenges and disadvantages associated with these interventions. Implementing and sustaining long-term behavioural changes can be arduous due to a variety of factors, including limited access to healthy food options, lack of social support, and individual barriers such as time constraints and competing priorities. Additionally, the complexity of human behaviour and the ingrained nature of unhealthy habits make it difficult to achieve lasting changes in lifestyle, requiring ongoing support and tailored interventions to overcome these obstacles (Alberti et al., 2007; Dunkley et al., 2014; Sami et al., 2017).

2. Screening for T2D and prediabetes

Screening, according to the World Health Organisation (WHO), is a sorting process aimed at identifying individuals that probably have a certain condition, and are thus never completely accurate by definition (WHO Regional Office for Europe, 2020). Screening tests allow to determine who is at risk before the onset of clinical symptoms and start the intervention earlier than without the screening programme, which may improve health outcomes for individuals. However, screening requires resources when it comes to time and equipment in the healthcare system, and may therefore not always be cost-effective, especially if no adequate and effective treatment can be offered to those identified by the test (WHO Regional Office for Europe, 2020).

Wilson and Junger (1968) have developed ten principles of screening, which are commonly referred to when defining whether screening is a suitable instrument to improve public health (WHO Regional Office for Europe, 2020). These principles of early disease detection include:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.

3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project. (Wilson & Junger, 1968, pp. 26–27)

Early detection and timely intervention are one key approach in managing T2D and prediabetes and in mitigating the adverse effects of these conditions. As the WHO points out, the early identification and treatment of precursors of a disease and thus the reduction of the disease incidence are a key goal of screening campaigns (WHO Regional Office for Europe, 2020). Approaches incorporating screening mechanisms and interventions aimed at patients with prediabetes have been shown to be effective, though the magnitude is highly dependent on the accuracy of the screening test that is selected (Barry et al., 2017).

Test performance can be measured by test sensitivity – the ability of a screening test to report a positive result for people with the condition – and test specificity – the ability of a test to report a negative result for people without the condition (WHO Regional Office for Europe, 2020). If a screening test comes back as positive, there is a certain probability that the person has the condition they were screened for and the test is a true positive, but it may also be a false positive result, since screening tests are not perfectly accurate. The same logic is true for negative results. If false negative results should be avoided and the cut-off value for a positive screening test is lowered, this comes at the expense of more false positive screening tests. Therefore, selecting a suitable screening strategy is a trade-off between test sensitivity and specificity, and the threshold value that is selected may vary depending on the specific goals of the screening programme (WHO Regional Office for Europe, 2020).

Various screening strategies have been developed to identify individuals at risk or who present with prediabetes and T2D, including fasting plasma glucose (FPG) test, oral glucose tolerance test (OGTT), random plasma glucose (RPG) test, and HbA1c tests. The FPG test is widely

accessible, relatively inexpensive, and easy to perform. It measures blood glucose levels after an overnight fast of at least eight hours. A glucose level of ≥126 mg/dL (7.0 mmol/L) on two separate occasions indicates diabetes, while values between 100-125 mg/dL (5.6-6.9 mmol/L) suggest prediabetes. However, the FPG test requires fasting, and its accuracy can be influenced by day-to-day glucose fluctuations (American Diabetes Association, 2014; World Health Organization, 2019). FPG tests have a test sensitivity of 64.1% (95% CI [61.7, 66.5]) and 54.5% (95% CI [52.5, 56.5]) and a test specificity of 65.4% (95% CI [63.0, 67.8]) and 100% (95% CI [100, 100]) for T2D and prediabetes, respectively (Hu et al., 2010).

The OGTT is more sensitive than the FPG test in detecting IGT. It involves assessing glucose levels two hours (2-h PG) after consuming a glucose-rich beverage. A blood glucose level of ≥200 mg/dL (11.1 mmol/L) confirms diabetes, while values between 140-199 mg/dL (7.8-11.0 mmol/L) indicate prediabetes (American Diabetes Association, 2014; World Health Organization, 2019). The OGTT provides information on both fasting and postprandial glucose levels but requires greater patient commitment, since it has been described as more uncomfortable for patients and requires at least 2 hours to perform, implying higher time costs for patients to be tested (Bennett et al., 2007). OGTTs tests have a test sensitivity of 81.1% and 93.0% and a test specificity of 100% and 100% for T2D and prediabetes, respectively (Aekplakorn et al., 2015).

The RPG test measures blood glucose levels at any time of the day, regardless of fasting. It can be valuable in identifying undiagnosed diabetes during acute medical care. A glucose level of ≥200 mg/dL (11.1 mmol/L), along with classic symptoms of diabetes, supports a diagnosis. However, the RPG test is less commonly used for screening purposes and may be influenced by recent food intake or stress (American Diabetes Association, 2014; World Health Organization, 2019).

The HbA1c test has gained recognition as a valuable screening tool for type 2 diabetes and prediabetes. It reflects average blood glucose levels over the past two to three months, providing a long-term assessment of glycaemic control. The American Diabetes Association recommends an HbA1c value of ≥6.5% (48 mmol/mol) for diagnosing diabetes, while values between 5.7% (39 mmol/mol) and 6.4% (46 mmol/mol) indicate prediabetes (American Diabetes Association, 2014; World Health Organization, 2019). HbA1c tests have been reported at a test sensitivity of 66.2% (95% CI [63.8, 68.6]) and 81.0% (95% CI [79.4, 82.6]) and a test specificity of 51.0% (95% CI [48.5, 53.5]) and 81.0% (95% CI [79.4, 82.6]) for T2D and prediabetes, respectively (Hu et al., 2010). Combining FPG and HbA1c tests increases the test

of detecting undiagnosed T2D to 96.5% (Hu et al., 2010). The HbA1c test offers several advantages over other screening strategies. It does not require fasting, making it more convenient for patients and facilitating population-based screenings. Moreover, HbA1c measurements are standardized and have demonstrated good reproducibility. The test is less affected by acute conditions and can be performed at any time during the day. However, it may not be suitable for certain populations as its accuracy can be limited in certain medical conditions(Bennett et al., 2007).

A key aspect of designing a successful screening campaign is to identify the most suitable target population. This should be grounded in the best available evidence to ensure all individuals for which screening is relevant are included, but the efforts of identifying cases is still economically balanced with healthcare spendings as a whole (WHO Regional Office for Europe, 2020; Wilson & Junger, 1968).

One way to ensure addressing the right target population in screening for prediabetes and T2D may be by involving questionnaires and risk scores to determine the population at particularly high risk for developing or presenting with T2D. These pre-screening methods may help to reduce costs by only performing screening tests when medically indicated, and avoid the discomfort and time involved in population-based screening approaches for individuals that are very unlikely to benefit from these procedures (Gillett et al., 2015; Mühlenbruch et al., 2020). Combining risk scores calibrated to an optimal cut-off point with screening methods has the potential to improve the cost-effectiveness of screening campaigns and lifestyle interventions aimed at preventing T2D (Mühlenbruch et al., 2020). The German Diabetes Risk Score (GDRS) is one of these risk scoring systems that calculates an individual's statistical estimate of the 10-year risk of developing type 2 diabetes. It utilizes anthropometric data, lifestyle information, and family history to provide an objective assessment of risk, and can be used both in preventive settings and during doctor-patient conversations for risk estimation (Schiborn et al., 2022).

Screening, if not based on suitable evidence and considerations, also bears the risk of leading to overdiagnosis of a condition. This implies that cases are detected, that would not have done any harm to the affected individual (WHO Regional Office for Europe, 2020). This may be the case if the condition that is being screened for tends to be latent or resolve itself, or if individuals are screened up to a very high age, when the competing risks of dying from other causes than the condition of interest outweigh the potential benefit of the screening

programme. Overdiagnosis is hard to be quantified, but needs to be considered when planning a screening programme (WHO Regional Office for Europe, 2020).

Even with the ideal screening test and population of interest for the screening programme selected, encouraging participation in the programme can be an issue. Communication of a screening programme to the population of interest is crucial to increase the uptake of the offer, but background characteristics of individuals also play an important role (WHO Regional Office for Europe, 2020). Studies have shown that a lower socioeconomic status and lower education levels are associated with a reduced likelihood of attending screening programmes (Linne et al., 2014; Maheswaran et al., 2006; WHO Regional Office for Europe, 2020). Additionally, individuals that are single or divorced, live further away from testing sites, or those who have recently immigrated are less likely to get tested (Linne et al., 2014; Maheswaran et al., 2006). A key issue in screening is that those who do not take up the offer of getting screened tend to have poorer health than individuals who decide to get screened, which negatively affects the effectiveness of these programmes (Linne et al., 2014; Maheswaran et al., 2006). Simmons et al. (2011) found that mortality rates of participants in a screening programme for T2D in the United Kingdom have a significantly lower mortality than a control group that was not invited for screening, but those who were invited and did not take up the offer had a significantly higher mortality rate. This difference also indicates that participation rates among different groups are not random, and that important background characteristics of individuals determine how likely they are to get screened.

3. Complications and healthcare costs of T2D

Managing glycaemic levels is important to slow down the disease progression of T2D and prediabetes, or even reverse pathological glucose levels and insulin resistances (DeFronzo et al., 2015).It is important to also include complications when analysing interventions that target T2D because of the implications they have on healthcare utilization, mortality and quality of life (Chatterjee et al., 2017).

T2D increases the risk of microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy. Diabetic retinopathy can lead to vision impairment and blindness, nephropathy affects the kidneys and can lead to end-stage renal disease, while neuropathy can cause sensory loss, pain, and foot ulcers, increasing the risk of lower extremity amputations (Chatterjee et al., 2017; DeFronzo et al., 2015). Macrovascular complications associated with T2D include cardiovascular disease, stroke, and peripheral arterial disease

(Chatterjee et al., 2017; DeFronzo et al., 2015). Individuals with T2D are also prone to developing metabolic syndrome, which includes abdominal obesity, hypertension, dyslipidaemia, and insulin resistance, further increasing the risk of cardiovascular disease (DeFronzo et al., 2015). Mental health issues, such as depression and anxiety, are more prevalent among individuals with T2D and can negatively impact quality of life (Mezuk et al., 2008).

T2D in itself and in the light of these complications imposes substantial healthcare costs. Expenses related to medications, regular check-ups, and diabetes-related hospitalizations contribute significantly to healthcare expenditures. Moreover, individuals with T2D often experience reduced productivity due to absenteeism, presenteeism, and disability, resulting in indirect costs for employers and society as a whole (Dall et al., 2010; Zhuo et al., 2014). The complications arising from T2D, both microvascular and macrovascular, lead to increased healthcare utilization and costs. Treating complications such as diabetic foot ulcers, renal dialysis, or cardiovascular interventions significantly contributes to the overall economic burden (Dall et al., 2010). Lifestyle modifications, including dietary changes, increased physical activity, and medication adherence, are essential for managing T2D but may come with associated costs such as purchasing healthier food options, gym memberships, or professional support (Lindström et al., 2006; Tuomilehto et al., 2011).

4. Theoretical framework

4.1. Cost-effectiveness analyses

This thesis is based on a cost-effectiveness analysis (CEA) which provides a framework to compare the health and economic consequences of two or more interventions, such as the cost and impact of two potential healthcare programs in the context of T2D prevention. Given the limited availability of data, often confined to small randomized controlled trial groups or reliant on observational data, modelling approaches become essential to comprehensively capture the intervention's benefits and costs. These models enable the estimation of expected costs and effects while accommodating the inherent uncertainty of the decision-making process. Additionally, they allow for the testing and comparison of different assumptions with relative ease (Drummond, 2007). Modelling is also relevant when it comes to examining the cost-effectiveness of screening strategies, which is a key aspect of this thesis. Screening programmes come with different, competing options about screening intervals, the population being screened, and the logistics of implementing the screening test. Modelling allows to

compare the cost-effectiveness of these strategies to each other and identify the optimal design of the screening programme without having to roll all of them out in the real world.

To assess the costs and effects of treatment B in comparison to treatment A, which may be the current standard of care, a feasible treatment alternative or a „do nothing"-alternative, a CEA can be conducted as a commonly used approach in health economic modelling. This analysis entails comparing the incremental costs and effects of both treatments, thereby calculating an incremental cost-effectiveness ratio (ICER)(Briggs et al., 2006; Drummond, 2007). The ICER quantifies the additional costs incurred to achieve one unit of outcome improvement by opting for the new treatment instead of the current standard of care. By utilizing quality-adjusted life years (QALYs) or other relevant metrics like T2D cases averted or weight lost during the intervention, depending on the data availability and modelling objectives, the effects can be expressed appropriately (Drummond, 2007).

$$ICER = \frac{(Total\ costs\ treatment\ B) - (Total\ costs\ treatment\ A)}{(QALYs/effects\ treatment\ B) - (QALYs/effects\ treatment\ B)} = \frac{\Delta Costs}{\Delta Effects}$$

Should the incremental costs be negative and the incremental effects positive, treatment B would dominate treatment A, establishing it as the preferred strategy. Conversely, if the incremental costs are positive and the incremental effects negative, treatment A would always be preferable to treatment B. However, if none of these scenarios arises and the ICER is positive, a clear dominant strategy does not emerge. In such cases, alternative decision rules need to be employed to determine the programs that yield optimal outcomes for patients, while simultaneously considering the budget constraints inherent in healthcare systems. One viable option is to compare the results of the CEA against a willingness-to-pay (WTP) threshold—a monetary value representing the amount society or the healthcare system is willing to pay for an additional QALY. These thresholds, which can be found in guidelines for economic evaluations of healthcare programs, assist in determining the cost-effectiveness of various programs within specific contexts (Briggs et al., 2006; Drummond, 2007).

Decision analytic models such as Markov models or state transition models have been developed to facilitate decision-making under uncertainty, and their input parameters involve a degree of uncertainty in many cases. The advantage of such models is that this uncertainty can be incorporated and accounted for, which makes them a transparent approach even if some input parameters are ambiguous (Briggs et al., 2006). To account for the uncertainty around input parameters, probabilistic sensitivity analyses (PSA) are a frequently employed tool in health economic modelling. If input parameters are associated with a certain degree of

unreliability or variability, this also has implications for the confidence in the outcome of the analysis. Since obtaining more information before performing the analysis may not always be a feasible option, PSAs offer an alternative by showing a range of outcomes that may be generated if input parameters vary. To do so, input parameters are assigned with a suitable probability distribution (Briggs et al., 2006). A large number of iterations is then performed, where during each iteration a new sample of parameters is drawn from the distributions to show an empirical distributions of ICERs (Drummond, 2007).

4.2. Microsimulation models for decision sciences

Computer models play a crucial role in assessing the effectiveness, costs, complications, and quality of life improvements related to screening, lifestyle interventions, and treatments in healthcare. Although Markov or semi-Markov chains have commonly been used to model the progression of diabetes in individuals or populations, microsimulation models (i.e. individual-based models) offer distinct advantages in the context of prediabetes lifestyle interventions.

Microsimulation models incorporate individual heterogeneity and enable the comparison of efficacy and cost-effectiveness of various interventions in the populations of interest (Krijkamp et al., 2018; Willis et al., 2020). These models take into account individual-level data to determine transition probabilities between health states, allowing for personalized simulations that reflect unique demographic characteristics (Khademi et al., 2019; Krijkamp et al., 2018). Additionally, microsimulation models simulate the entire life history of each individual, facilitating the exploration of optimal age ranges for different screening options and interventions (Willis et al., 2020).

Healthcare policy makers rely on decision modelling tools to guide resource allocation decisions. State-transition cohort models are commonly used for this purpose but have inherent limitations. Deterministic cohort models assume that transition probabilities depend only on the current health state, while microsimulation models can reflect individual clinical pathways, incorporate the impact of history on future events, and capture baseline variation in patients' characteristics. Microsimulation models simulate the impact of interventions or policies on individual trajectories, allowing for stochastic variation in disease progression and individual-specific characteristics. They address the limitations of cohort models and introduce "memory" to reflect the impact of duration spent in a diseased state (Eom & Li, 2020; Khademi et al., 2019; Krijkamp et al., 2018).

Microsimulation models, while providing additional functionality and accuracy, also present numerical and computational complexity. High-level programming languages like R offer computational efficiency and integration of advanced statistical analyses (Krijkamp et al., 2018). Another drawback of individual patient-level simulations are limitations in the flexibility of these models to assess parameter uncertainty. While one of their core elements involves modelling variability in patients and events, though input parameters remain static for the entire patient cohort. Sensitivity analyses or other methods of assessing decision uncertainty such as value-of-information analyses can get computationally difficult to perform if large sets of patients are being simulated (Briggs et al., 2006).

The use of individual-level simulation model has been frequently employed in the research of T2D prevention and treatment strategies. Oftentimes, these models are based on large datasets and offer the advantage of making use of this rich data, that allows to calculate for individual patient characteristics and disease pathways (Briggs et al., 2006). An example for the use of a microsimulation model in the disease area of T2D is a model based on the United Kingdom Prospective Diabetes Study (UKPDS) (Clarke et al., 2004). This model initializes a data set of patients with specific background characteristics and, based on these, risk equations for T2D and associated outcomes. Over the time horizon of the model, patients event and risk factor equations are run for each patient, updating their history of diabetes-related events and individual risk factors in every cycle (Briggs et al., 2006; Clarke et al., 2004). A similar approach of constructing a microsimulation model will be used in this thesis.

5. Modelling studies for T2D prevention and prediabetes

Several researchers have developed models to investigate the cost-effectiveness of interventions aimed at prediabetes and preventing T2D. Both Markov cohort models and microsimulation models were used to perform CEAs. Both of these types of models commonly focus on preventive strategies targeting high-risk individuals or the population as a whole, or on screening strategies to facilitate the early detection of T2D (Gillett et al., 2015). However, models vary considerably in how they define the target population, whether and which adverse events (AEs) associated with T2D are considered in the model, and which screening and intervention strategies they combine. There is no gold standard to be used in T2D prevention evaluations, which often complicates the comparability of results. A few paper that have informed the development of the paper used in this thesis are briefly summarized in the following.

In a study by Neumann et al. (2017),the researchers aimed to estimate the cost-effectiveness of a T2D prevention program targeting weight reduction, increased physical activity, and a healthier diet in individuals in a prediabetic state, differentiating between IGT, IFG and a combination of both, in a Swedish setting. They used a Markov model to compare the cost-effectiveness of the intervention versus no intervention. The analysis was done deterministically and probabilistically for different scenarios based on sex and age groups. The results showed that all interventions were cost-effective, ranging from 3833 €/QALY gained to 9215 €/QALY gained. This model did not incorporate any screening method to establish the cost-effectiveness of the behavioural intervention.

Palmer et al. (2004) developed an Internet-based, interactive computer model called the CORE Diabetes Model to determine the long-term health outcomes and economic consequences of implementing different treatment policies or interventions for type 1 and type 2 diabetes mellitus. The model incorporates various sub-models representing complications of diabetes and uses Markov models with Monte Carlo simulation to project outcomes for populations. The model allows for the calculation of complications, life expectancy, quality-adjusted life expectancy, and total costs within populations. It can be customized to different cohorts and can incorporate new data as it becomes available. This model is frequently used to model T2D interventions, though it is less common in modelling prevention strategies.

Liu et al. (2013) conducted a study in China to explore the clinical and economic outcomes of strategies to prevent diabetes in a developing country setting. They used a hybrid decision tree Markov model to compare the long-term clinical and economic outcomes of four diabetes prevention strategies with a control group. The strategies included screening for undiagnosed diabetes and impaired glucose tolerance (IGT) with lifestyle interventions on diet, exercise, or both, as well as one-off screening alone. The study found that all simulated screening programs prolonged life expectancy, postponed the onset of diabetes, and increased QALYs. Prevention programs were also associated with cost savings compared to the control group, especially in the population aged 25 years. However, cost savings were reduced when screening was affected by poor performance and non-compliance.

Goel et al. (2018) focused on the analysis of diabetes follow-up using multi-state Markov models. They assessed the importance of HbA1c as a disease marker for T2D using a three-state Markov model. The study included 246 diabetic patients and analysed transition probabilities, mean sojourn time in each state, and expected state-specific survival time. The

results showed that once a patient entered the diabetic state (HbA1c > 6.4), the chances of returning to a normal or pre-diabetic state were very small.

Roberts et al. (2018) examined the costs and effects of different intensity lifestyle programs and metformin in individuals with intermediate categories of hyperglycaemia in the UK. They developed a decision tree and Markov model to compare low-intensity and high-intensity lifestyle programs, metformin, and no intervention. The study found that low-intensity lifestyle programs were the most cost-effective, followed by high-intensity lifestyle programs and metformin. The programs were particularly cost-effective in individuals with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).

Walker et al. (2015) used a Markov model to investigate the integrated effect of lifestyle changes (weight loss, dietary patterns, and increased physical activity) and genetic susceptibility on changes in glycaemic control in overweight or obese participants. The study demonstrated the importance of modifiable factors related to body weight, diet, and physical activity in impacting the development of T2D.

The study by Gillet et al. (2015) compared the cost-effectiveness of screening for type 2 diabetes using HbA1c versus FPG tests within the NHS Health Checks program in England. Based on data from a multi-ethnic population, HbA1c testing was found to be more cost-effective than FPG testing, resulting in cost savings and improved QALYs when a risk score was used for pre-screening. The study highlighted the importance of considering regional variations and uptake rates when determining the optimal screening strategy.

This thesis combines elements of several studies described above. A microsimulation state transition model was selected to show variation in individual characteristics and treatment effects. In contrast to many other papers, this model will assess the cost-effectiveness of a screening programme in combination with a lifestyle intervention targeted at patients with prediabetes, to capture all relevant costs and effects of an extensive programme aimed at preventing T2D. Details on methodology and results will be presented in part II.

Part II: Research paper

Development of a microsimulation model to evaluate the cost-effectiveness of screening and a lifestyle intervention for prediabetes

Abstract

Background and Motivation This paper develops a microsimulation model to assess the health and economic outcomes of implementing a prediabetes screening programme in Germany in combination a lifestyle intervention. It addresses the lack of comprehensive models in T2D prevention research and promotes transparency by sharing the model's code for further development.

Methods The methods of the study involve the development of a microsimulation state transition model to assess the cost-effectiveness of a population-based screening program and a behavioural intervention for individuals at risk of type 2 diabetes (T2D) compared to the current standard of care in Germany. The individual-level model considers different health states, transitions, and outcomes related to T2D. The analysis uses a societal perspective, including direct and indirect costs, and employs incremental cost-effectiveness ratios (ICERs) to compare the interventions. Transitions probabilities are a function of HbA1c levels and are thus individual-specific. The screening programme involves HbA1c blood tests, and the lifestyle intervention is based on the German Prediabetes Lifestyle Intervention (PLIS) trial.

Results The base case analysis of screening and treatment for prediabetes resulted in an incremental cost of €18,840 and an additional 0.57 quality-adjusted life years (QALYs) gained, with an incremental cost-effectiveness ratio (ICER) of €33,052 per QALY gained compared to no screening and no intervention. The intervention group showed a higher remission rate and fewer adverse events compared to the standard of care. The ICER changed significantly when the duration of the intervention effect was varied in scenario analysis, indicating a strong impact of this parameter on cost-effectiveness.

Conclusions This model provides the framework and a first exploratory analysis of a microsimulation focussed on screening and treatment of prediabetes. Scenario analysis showed a large impact of the underlying assumptions on treatment effects and epidemiologic data on the outcomes. This highlights the need for further research to obtain reliable data representing the population of interest to estimate the cost-effectiveness of a programme like this being rolled out on a population level.

1. Introduction

Type 2 diabetes (T2D) prevalence in Germany, as in many Western countries, has been steadily increasing and is posing a considerable strain on healthcare systems. As of 2010, 7.4% of men and 7.0% of women aged 18 to 79 in Germany were diagnosed with T2D. It is estimated that at least an additional 1.2% of women and 2.9% of men have undetected T2D, especially in early stages of the disease when the clinical presentation is ambiguous (National Diabetes Surveillance at the Robert Koch Institute, 2019; Tamayo et al., 2016). Incidence rates are rising, with some projections estimating T2D cases to double between 2010 and 2040 (Voeltz et al., 2022). Annual direct healthcare costs of 3,352 € per patient with diabetes, and additional indirect costs of more than 4,000 €, pose a considerable burden on the German society (Ulrich et al., 2016). T2D is also associated with increased incidence rates of a set of complications, including stroke, renal disease and cardiovascular diseases (CVDs) (Glechner et al., 2018; International Diabetes Federation, 2021; Selvin et al., 2010).

Considering current and future burden, the prevention of T2D is imperative for the sustainability of healthcare systems. Clinical studies have shown that the disease can be effectively prevented through lifestyle modifications, weight loss and increased physical activity (Alberti et al., 2007; DeFronzo et al., 2015; Tuomilehto et al., 2011). These risk reductions also persist beyond the active intervention and thus sustainably affect participants' health outcomes. Given budget constraints in the healthcare system, many countries also require the explicit consideration of costs as compared to the health benefits yielded by the intervention. Several health economic analyses have found lifestyle intervention programmes aimed at preventing T2D to be cost-effective (Breeze et al., 2017; Saha et al., 2010; Uusitupa et al., 2019; Watson et al., 2014).

Screening for prediabetes and T2D can be conducted by analysing fasting plasma glucose (FPG), 2-hour post-challenge glucose (2-h PG) following an oral glucose tolerance test (OGTT), or glycated haemoglobin A1c (HbA1c). In contrast to 2-h PG and FPG, HbA1c provides a reflection of long-term glycemia and represents average blood glucose levels over the past two to three months (American Diabetes Association, 2014). Guidelines provide different cut-off values which serve as a diagnostic criteria for prediabetes and T2D (American Diabetes Association, 2014; International Diabetes Federation, 2021; World Health Organization, 2019). However, blood sugar levels and HbA1c need to be viewed as a risk continuum, with complications and adverse effects on blood vessels increasing steadily. Therefore, 2-h PG, FPG and HbA1c levels just under the threshold qualifying as T2D are commonly grouped as

prediabetes, defining individuals at particularly high risk of developing T2D in the future (American Diabetes Association, 2014). In order to target these populations at risk, patients with prediabetes are most frequently targeted by lifestyle interventions to prevent further deterioration of their glycaemic control.

Several researchers have conducted cost-effectiveness analyses of T2D prevention programmes, but the structures of these models vary. There is no consensus on whether screening for prediabetes and which adverse events are to be included in the model, which negatively impacts comparability of outcomes (Watson et al., 2014).

The German Prediabetes Lifestyle Intervention Study (PLIS) provided new insight into the effectiveness of a lifestyle intervention targeting patients with prediabetes. It makes use of a risk stratification to provide more intensive treatment to patients at particularly high risk of developing T2D, which proved to be successful in improving patient outcomes in the trial (Fritsche et al., 2021). The outcomes of the PLIS trial serve as a basis to developing a microsimulation model including screening strategies and adverse events associated with T2D prevention aimed at capturing the full effects of a prediabetes lifestyle intervention.

The aim of this paper is the development of a microsimulation state transition model to project the health and economic outcomes associated with implementing a prediabetes screening program in Germany compared with current practice. It simulates a patient cohort reflecting the background characteristics of the German population, and then applies a lifestyle intervention programme as described by Fritsche et al. (2021) to patients with prediabetes. Based on the PLIS study, a first exploratory analysis of the cost-effectiveness will be performed.

While there have been several studies examining the cost-effectiveness of screening programmes for (pre-)diabetes or lifestyle interventions to prevent T2D, very few combine both interventions in a joint model. Furthermore, the publication of the code that was used to develop the model in the appendix allows researchers to make use of this code and develop it further, which is a first step towards making T2D prevention models more comparable and transparent.

2. Methods

2.1. Analytic overview and setting

We developed a microsimulation state transition model to conduct a cost-effectiveness analysis of a population-based screening programme combined with a behavioural T2D

prevention programme for at-risk individuals, compared to no screening and no intervention – the current standard of care in Germany. Screening is applied to individuals over the age of 35 and with a body mass index (BMI) of at least 25. Model outcomes include the duration spent in a diabetic or prediabetic health state, return to normal glucose tolerance (NGT) and the incidence of selected adverse events associated with T2D. The current model reflects the population of the PLIS trial, implying that age and HbA1c distributions do not reflects the whole German population because of data limitations. The microsimulation model can easily be tailored to other populations and contexts by adapting the code provided in appendix A.

In line with the guidelines for cost-benefit analyses (CBA), this analysis will employ a societal perspective in the base case scenario, including direct and indirect medical costs as well as participants' time and productivity costs (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2022). This perspective is relevant, since intervention is targeted at individuals that are partially still in the workforce, and a behavioural intervention has potentially substantial impact on time costs and absence from work. Additional analyses will reflect outcomes from a healthcare perspective. We discounted costs and health benefits by 3% per year, in line with German guidelines (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2022).

Incremental costs and effects for all scenarios will be reported, as well as incremental cost-effectiveness ratios (ICERs), which quantify the additional cost in Euros for each additional quality-adjusted life year (QALY) gained of the lifestyle intervention to the current standard of care (Briggs et al., 2006). Additionally, an analysis of individuals returning to normal glucose tolerance and adverse events in the intervention and control group will be provided for the base case analysis described in section 2.5.

CEAs in the German context are not compared to a willingness-to-pay (WTP) threshold but ranked in an "efficiency border" comparing all available, authorized alternatives within a disease area are graphically compared to the intervention that is to be investigated. Interventions are being ranked according to their respective costs and utilities and then ranked in a two-dimensional space. The efficiency border then connects the most cost-effective treatment to the next best alternatives, setting the threshold which needs to be surpassed by a new strategy to be considered cost-effective. This leads to varying thresholds for each disease area (Foos et al., 2010; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2022). This approach is frequently debated, arguing that it is not in line with equity considerations in a solidaric healthcare system (Verband Forschender Arzneimittelhersteller

e.V., 2009). Additionally, assessing all alternatives in the disease area is out of the scope of this paper. Therefore, results will be presented in the form of ICERs without comparing the to a WTP threshold and thus making conclusions about the cost-effectiveness of the intervention in the German context.

All data analysis and visualisation were performed in R.

2.2. Model structure

The microsimulation state transition model used in this paper consists of seven mutually exclusive and collectively exhaustive health states: normal glucose tolerance (NGT), undetected prediabetes (PD(ud)), detected prediabetes with a lower risk of developing type 2 diabetes (PD(dLR)), detected prediabetes with an increased risk of developing type 2 diabetes (PD(dHR)), undetected type 2 diabetes (T2D(ud)), detected type 2 diabetes (T2D(d)), and death (D). Health states are differentiated from each other based on predefined HbA1c cut-offs (American Diabetes Association, 2014; World Health Organization, 2019). Individuals with an HbA1c value of < 5.7% (39 mmol/mol) are placed in NGT, and those with a value of ≥ 6.5% (48 mmol/mol) are placed in one of the T2D states. Everyone with an HbA1c between 5.7% (39 mmol/mol) and 6.4% (46 mmol/mol) occupies one of the PD states. Individuals are first moved to an undetected health state if they transition within a given cycle. They can then transition to a detected health state within the same or a following cycle if they are identified through the screening programme, or if an adverse event occurs. In this case, the health state is updated to a detected state. If individuals with prediabetes are detected by screening, they are separated into a high-risk and low-risk group based on their liver fat content (LFC). In line with the PLIS trial, a threshold of 5.56% serves as a threshold for this classification (Fritsche et al., 2021).

Each year, individuals with T2D or prediabetes can move into remission and return to the NGT health state, however patients with both T2D(d) and T2d(ud) must transition through PD(dLR or dHR) and cannot directly move to NGT. Transition probabilities are a function of HbA1c levels. Death is an absorbing health state. An illustration of all possible transitions between health states can be found in Figure 1. A more extensive Markov decision tree with all possible transitions is illustrated in appendix B.

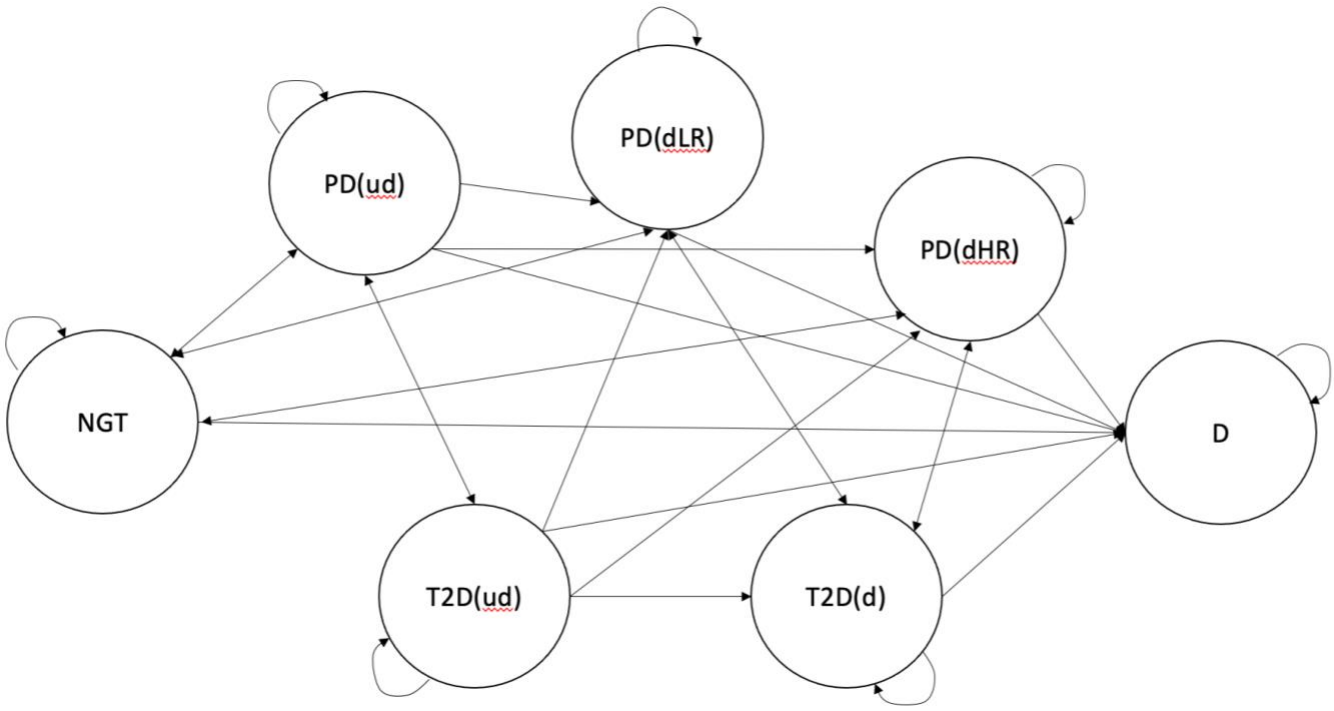

Figure 1: possible transitions between health states

In addition to the disease history moving through health states, the model also simulates adverse events. Adverse events can occur in all health states except death, but the probability is higher in patients with T2D and higher HbA1c values. All adverse events are associated with costs and disutilities, which are added in the respective years they occur in. Events incorporated in this model can be divided into chronic events and one-off events.

Chronic events considered in this model are congestive heart failure (CHF), end-stage renal disease including dialysis, serious eye disease (blindness), and stroke. These events have long-lasting impact on patients' lives and thus costs and utility decreases associated with them are applied in all years following the initial event. In contrast to that, one-off events can happen repeatedly and impact patients' quality of life (QoL) for a limited time. Therefore, costs and disutilities for these events are only incorporated in each year the event occurs for a given individual. Foot ulcers, unstable angina pectoris and myocardial infarctions are one-off adverse events considered in this model.

To set up the microsimulation, a patient cohort of 5,000 patients is generated and all patients are randomly assigned a gender, HbA1c value, 2-h PG, and liver fat content based on the distributions reported in the PLIS trial. In line with the mean age in the trial, all patients enter the model at age 58 (Fritsche et al., 2021). The simulated HbA1c value serves as a basis for the

initial health state allocation. All individuals start off in an undetected health state (NGT, PD(ud) and T2D(ud)) and can transition in yearly intervals until death. If patients move to a different health state, their HbA1c values are updated to a randomly generated values within the boundaries of the corresponding health state. HbA1c levels for undiagnosed prediabetes are higher, since glycaemic control in this group is not managed through medication or lifestyle modifications. This also implies a higher risk of adverse events occurring in this group.

2.3. Intervention and comparator

2.3.1. Screening

Given that no screening programme for prediabetes is currently in place in Germany, a hypothetical screening programme was developed for this model. For this purpose, it was assumed that an HbA1c blood test is incorporated in the Health-Check-up 35 (Gesundheits-Check-up 35), which is offered every three years to all citizens enrolled in public health insurance over the age of 35 (Deutsches Statistisches Bundesamt, n.d.).

While the PLIS trial used 2-hour post-challenge glucose after a standardised OGTT (Fritsche et al., 2021), we selected HbA1c as a diagnostic tool for prediabetes, since it is cheaper than the OGTT (Kassenärztliche Bundesvereinigung, 2021), and less unpleasant for patients as it can be incorporated with blood tests that are routinely conducted during health check-ups, which makes it a suitable tool for large-scale screening (Bennett et al., 2007). However, it needs to be considered that HbA1c has a lower test sensitivity for T2D, and the difference is even more pronounced in prediabetic patients (Bennett et al., 2007; Gillett et al., 2015; Hussain, 2016). Due to data constraint, this model uses HbA1c only as a primary screening tool. If a screened patient presents outcomes which would qualify as T2D, they are re-tested with an OGTT, and test sensitivities for both tests are considered. This implies that not all patients participating in the screening programme may be identified as prediabetic or diabetic, respectively, and may thus remain in an undiagnosed health state in following cycles. Using HbA1c as a diagnostic tool for a prediabetes screening programme without any further re-tests and combining it with an OGTT for patients within a HbA1c range indicating T2D was also validated in by confirming the screening set-up and modelling structure with experts in this field, Sabrina Schlesinger (German Diabetes Centre), Damon Mohebbi (University Clinic Düsseldorf), and Matthias Schulze (German Institute of Human Nutrition).

2.3.2. Lifestyle intervention

Once identified with prediabetes, the model applies a lifestyle intervention programme as described by Fritsche et al. (2021). Individuals identified by the screening strategy were categorized into a high- and low-risk group in line with PLIS (Fritsche et al., 2021). Both groups underwent a lifestyle treatment with the duration of one year, but the treatment was intensified for the high-risk group. The intensive lifestyle treatment involves 16 lifestyle coaching sessions of 30-60 minutes within the 1-year intervention period and an advised 6 hours of exercise per week, compared to 8 lifestyle coaching sessions and 3 hours of exercise per week in the conventional lifestyle intervention.

In the absence of prediabetes screening, prediabetes in Germany would not be detected or treated. However, patients with T2D may still be diagnosed through random clinical discovery or by developing adverse events and then undergo standard treatment.

The microsimulation does not model any direct effect on patients with T2D, but it modulates the number of patients with T2D through the preventive effect of the treatment. Patients that develop T2D are still considered in the model with their respective costs and utilities as described below.

2.4. Data

2.4.1. Epidemiologic data

Transition probabilities within the model and the probability for developing adverse events are based on published data and estimations. The probabilities for progressing from NGT to PD and from PD to T2D are a function of HbA1c values and are thus individual-specific. The baseline incidence rates and hazard ratios (HR) for these calculations are displayed in table 1, transition probabilities that are not individual-specific are summarized in table 2. Mortality rates are adjusted for age, gender, and a hazard ratio for patients with T2D, as detailed in appendix C.

Table 1: Baseline incidence rates and HRs of developing PD and T2D		
Incidence rate of PD from NGT*	8.7	
Incidence rate of T2D from PD*	40.5	
	HR of developing (pre-)diabetes	95% CI
HbA1c < 5.0%	0.53	[0.40;0.69]
HbA1c 5.0-5.4%	1	
HbA1c 5.5-5.9%	1.8	[1.61;2.01]
HbA1c 6.0-6.4%	4.03	[3.52;4.61]
HbA1c >=6.5%	10.4	[8.80;12.28]

NGT = normal glucose tolerance, PD = prediabetes, T2D = type 2 diabetes; * incidence rates are expressed per 1000 person-years

based on Selvin et al. (2010), data extracted with PlotDigitizer, 3.1.5, 2023, https://plotdigitizer.com

Table 2: Non-individual specific transition probabilities per 1-year cycle	
Probability of regressing to NGT from PD	0.0028 [1]
Probability of regressing to PD from T2D	0.0028 [1]
Probability of random clinical discovery of T2D	0.1670 [2]
HR of mortality for individuals with T2D	1.8000 [2]

NGT = normal glucose tolerance, PD = prediabetes, T2D = type 2 diabetes, HR = hazard ratio

Data sources: [1] Karter et al. (2014), [2] Gillet et al.(2015), [3] The Emerging Risk Factor Collaboration (2011)01/06/2023 14:09:00

2.4.2. Screening

Using HbA1c blood tests as a screening tool, prediabetes was defined as values ≥ 39 mmol/mol and < 48 mmol/mol, and the cut-off for T2D is ≥ 48 mmol/mol. Any values lower than 39 mmol/mol are defined as normal glucose tolerance. The thresholds for this analysis are based on the classification of T2D and prediabetes by the American Diabetes Association (ADA) (American Diabetes Association, 2014; Rodgers et al., 2021). Values are defined by a single blood draw conducted during regular health check-ups in the base case scenario. Therefore, only the costs for the HbA1c test are added.

If HbA1c tests yield a result that indicates diabetes, patients are retested using an OGTT to confirm the diagnosis prior to starting treatment for T2D. In line with ADA guidelines, a 2-hour post-challenge glucose of 200 mg/dL following the OGTT confirms the diabetes diagnosis, and patients move to the T2D(d) health state (American Diabetes Association, 2014). The health

states used in the model are based on HbA1c values measured in patients, and thus each individual can be clearly assigned to one health state at each given time.

2.4.3. Lifestyle intervention

Patients were exposed to a lifestyle intervention in the model, stratified into a high- and low-risk group. A liver fat content of 5.56% served as a cut-off value for this classification. Individuals that participate in the lifestyle were assigned a randomly generated reduction of their HbA1c value based on the mean and standard error provided in the PLIS trial (Fritsche et al., 2021). This reduction is based on a normal distribution using mean values and 95% confidence intervals reported in PLIS (Fritsche et al., 2021), which is -1.5 [-1.8; -1.1] and -0.5 [-0.9;0.2] the high- and low-risk group, respectively. In the base case scenario, described in section 2.5, the treatment effect was maintained lifelong and thus the HbA1c value is only updated again if patients move to a new health state. Since the true continuance of the treatment effect is unknown, scenarios were created to show the spectrum of influence on different durations of the treatment effect.

2.4.4. Adverse events

The probabilities of developing these adverse events, as well as the costs and disutilities associated with them, are detailed in appendix C. The increased mortality caused by adverse events is lumped into a hazard ratio of 1.8 applied to mortality rates with T2D based on The Emerging Risk Factor Collaboration (2011). Adverse events as described in this section thus only encompass non-fatal events.

2.4.5. Utilities

Utilities for patients in the model are dependent on the health state they are in and which adverse events they experience at any given cycle. There is currently no evidence that patients with prediabetes have a reduced quality of life, even though they sometimes report poorer self-reported health during the first year after diagnosis compared to control groups (Herman et al., 2017). Therefore, utilities for patients with prediabetes was set to 1, equal to patients with NGT. Utilities and disutilities used in the model are summarized in table 3.

Table 3: Utilities and disutilities used in the microsimulation model, based on the EQ-5D questionnaire		
Utilities		
Normal glucose tolerance		1 [1]
Prediabetes		1 [1]
Type 2 diabetes (without complications)		0.965 [1]
Death		0 [1]
Disutilities of screening and adverse events	*frequency*	
screening test	one-off	-0.01 [2]
unstable angina pectoris	one-off	-0.18 [1]
coronary heart failure	chronic	-0.2 [1]
end-stage renal disease	chronic	-0.2 [1]
foot ulcer	one-off	-0.17 [1]
myocardial infarction	one-off	-0.18 [1]
blindness/serious eye disease	chronic	-0.16 [1]
stroke	chronic	-0.167 [1]
Data sources: [1] Kahn et al. (2010); [2] Goyder & Irwig (2000)		

2.4.6. Costs

For simplification purposes, a fixed amount was applied to all patients with diagnosed diabetes and prediabetes covering healthcare costs, and a separate sum of indirect costs was added in the societal perspective. In line with German guidelines, these indirect costs account for reduced productivity and indirect healthcare costs caused, which was applied to patients both in diagnosed and undiagnosed disease states. Cost parameters for patients with T2D were obtained from Ulrich et al. (2016), which represents the latest available data on the cost burden of T2D in Germany. In line with Neumann et al. (2017), the direct and indirect costs of prediabetes were estimated at 46% of those of patients with T2D. Indirect costs were applied to all age groups to avoid biased results in favour of younger patients when stratifying the analysis by age groups.

Costs for screening, healthcare visits and interventions were obtained from official German data sources (Kassenärztliche Bundesvereinigung, 2021; Verband der Privaten Krankenversicherung (PKV), 2013). Average wages for participants time costs, which were added for each of the 60-minute lifestyle coaching session and the weekly requirement for exercise, and the costs for providing the intervention are taken from the German Federal

Office for Statistics (Statistisches Bundesamt, 2021a). For equity reasons, wages were not varied based on gender to avoid biased results when stratifying results by gender.

Costs for adverse events are added in each year they occur, and for chronic events also in following years. A full table of all data sources, including explanations and calculations wherever applicable, can be found in the appendix C and in the R code in appendix A. All cost positions were indexed to 2021 to match the year of the publication of the PLIS paper using the harmonized consumer price index (Deutsches Statistisches Bundesamt, n.d.), reported in Euros.

2.5. Base case and scenario analyses

To reflect the uncertainty around certain aspects of the model, different scenarios were designed determine the possible scope of effects and costs given specified sets of assumptions. The aspects that were modified for this purpose include the analytic perspective, screening participation rates, whether the screening was embedded in an existing health check-up, adherence rates to the behavioural intervention, and the duration of the intervention effect on HbA1c values after completion of the treatment. The exact combination of parameter in each scenario is displayed in table 4.

Table 4: Base case scenario and scenario analyses in the model

	Base case	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Model set-up					
Analytic perspective	Societal[1]	Healthcare	Societal[1]	Societal[1]	Societal[1]
Screening					
Screening participation	100%	50%[2]	50%[2]	100%	100%
Screening frequency	Every 3 years	Every 3 years	Annually	Every 3 years	Every 3 years
Lifestyle intervention					
Duration of intervention effect	Life-long	Life-long	Life-long	7 years (gradual decrease)	Return to baseline after treatment ends

[1] According with German guidelines, the societal perspective includes time costs of participants and indirect costs associated with reduced productivity, prolonged absence from work and premature death (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2022).

[2] in line with reported participation rates in Gesundheitsberichterstattung des Bundes (2021)

Adherence to screening and the lifestyle treatment is defined as full participation in all affiliated activities within the model. For screening, this means that participants attend the health check-up in the suggested intervals and get the HbA1c test done, together with other routine blood work. Patients consequently also attend a follow-up visit to confirm their T2D diagnosis, if required. With regards to the lifestyle treatment, adherence implies that individuals participate in all activities as described by Fritsche et al. (2021). Even though it could be assumed that also partial participation (e. g. attending meetings irregularly or dropping out before the end of the intervention) may also yield benefits for participants and costs, these cases are not considered in this model.

2.6. Validation

To validate the model, the outcomes after two years were compared to the results of the PLIS trial with respect to the number of participants returning to NGT and adverse events they experienced. Additionally, we compared the outcomes to diabetes incidence rates to ensure our model is in line with official data in this regard. Additionally, extreme value checks were performed to ensure the model produces results that are in line with the expectations when

varying input parameters. A comprehensive list of all validation efforts and their results can be found in appendix D.

2.7. Probabilistic sensitivity analysis (PSA)

The code provided in appendix A for this model offers the possibility to perform probabilistic sensitivity analyses. This allows investigating how the model inputs are affected by uncertainty. The model currently performs 100 Monte Carlo iterations with varying input parameters for utilities, transition probabilities and costs. Utilities and transition probabilities follow a beta distribution. Cost parameters are subjected to a gamma distribution to ensure these parameters cannot take on negative values. To the extent possible, the parameters in the parametric distributions were informed based on the published source. In the absence of data on the standard errors for certain input parameters, a standard error of 15 % was assumed in cases where this information was missing. Input parameters selected for PSA and the results of the exploratory PSA analysis based on the PLIS trial can be found in the R code in appendix A and in the overview in appendix E.

3. Results

In the base case analysis, the screening and treatment of prediabetes cost and additional 18,840 € and provided an additional 0.57 QALYs, yielding an ICER of 33,052 € per QALY gained compared with no screening and treatment. Incremental costs were largely driven by the intervention cost.

In the base case analysis, we observed three times higher remission rate and substantially less adverse events in the intervention group. Detailed results on this are displayed in table 6.

Table 5: Lifetime incremental costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) per individual of the base case and scenario analyses

	Base case	*Scenario 1*	*Scenario 2*	*Scenario 3*	*Scenario 4*
Incremental costs	18,840 €	2,290 €	22,576 €	21,504 €	21,598 €
of which for screening	29€	21 €	74 €	32 €	27 €
of which for the intervention	18,841 €	1,161 €	19,312 €	19,025 €	19,143
Incremental effects	0.57	0.16	0.48	0.28	0.14
ICER	**33,052 €**	**14,250 €**	**48,034 €**	**76,800 €**	**154,271 €**

Table 6: Life-time occurrence of adverse events and remission to normal glucose tolerance in the base case scenario (per 5.000 individuals modelled)		
	Screening & lifestyle intervention	Standard of care
Total adverse events	139	176
unstable angina pectoris	42	51
coronary heart failure	38	44
end-stage renal disease	6	8
foot ulcer	12	19
myocardial infarction	26	34
blindness/serious eye disease	12	15
stroke	3	5
Return to normal glucose tolerance (remission)	781	255

When we varied the duration of the intervention effect beyond the intervention period in scenario analysis, we found that the ICER increases steeply, as illustrated in table 5. As this analysis shows, varying these aspects of the model has a large impact on the cost-effectiveness. When comparing the cost-effectiveness of scenario 5, where the treatment effect only lasted for one year upon completion of the intervention, to the base case scenario, assuming a life-long intervention effect, the ICER more than doubles.

4. Discussion

We developed a novel microsimulation state transition model to capture the costs and effects of a prediabetes lifestyle intervention based on the effects reported in the PLIS trial (Fritsche et al., (2021). By incorporating various elements from previously published papers on simulating prediabetes interventions, this model provides a comprehensive overview of the costs, utilities, and outcomes associated with screening, lifestyle intervention, and adverse events. To our knowledge, this is the first model that captures the effects of the PLIS trial in a microsimulation, and it is one of very few that include screening and a lifestyle intervention for prediabetes into a single model.

In the base case scenario, an additional life year obtained in the screening programme combined with the lifestyle intervention costs on average 33,052 €. ICERs in the scenario analysis vary between 14,250 € and 154,271 €. These findings highlight the potential effectiveness of the prevention programme in reducing the incidence of type 2 diabetes. By

identifying individuals at risk and providing appropriate interventions, the programme contributes to a significant improvement in disease remission rates and reduction of adverse events.

However, it is important to note that the base case analysis also revealed certain challenges associated with the intervention. Specifically, we observed a higher incidence of adverse events in the control group compared to the intervention group. This increase in adverse events was predominantly driven by foot ulcers and cardiovascular events. The impact of adverse events on the outcomes was found to be unstable when considering smaller numbers of individuals simulated. This instability suggests that rare events with large effects have a disproportionate influence on the results, emphasizing the need for robust sample sizes and careful consideration of event probabilities.

Data availability has been a critical challenge in the development of the microsimulation model. Information regarding crucial aspects such as the distribution of HbA1c levels in the entire population is scarce. As a result, assumptions have been made to estimate transition probabilities and the probability of adverse events in different health states. While these assumptions are based on the best available evidence, the limitations in data can affect the accuracy and generalizability of the model.

Many factors influence the probability of developing T2D, including age, gender, comorbidities, and genetic aspects (DeFronzo et al., 2015; Walker et al., 2015). Unfortunately, due to data availability issues, these variations could not be fully incorporated into the model. However, it is crucial to recognize the importance of considering these factors in future iterations of model development. By incorporating a broader range of factors, such as genetic predisposition and other relevant demographic characteristics, the model can provide a more comprehensive and accurate representation of the population and its susceptibility to T2D.

HbA1c levels have been clearly linked to T2D and prediabetes, and higher HbA1c values are linked to a greater likelihood of developing T2D, even though this association is not perfectly linear if FPG or 2-h PG following an OGTT are used as diagnostic tool (Diabetes Prevention Program Research Group, 2015). Therefore, HbA1c has been selected as a direct mechanism for diagnosis and treatment effects in this model. The use of HbA1c in screening for T2D and prediabetes is a more recent development, and therefore data in this regard is more scarce (DeFronzo et al., 2015; Rodgers et al., 2021). No data on the natural progression of HbA1c over an individual's lifetime irrespective of disease state was available at this point. Therefore, HbA1c was assumed to be linear and only updated if patients moved to a new health state or

participated in the lifestyle intervention. It is unclear whether this is an accurate description of the underlying biological mechanisms, but since this is the basis for all disease progression in this model, this may have implications on the outcomes provided in this model.

An important limitation of this model is that T2D rates and the risk of developing adverse events could not be adjusted for participants' age. Real world evidence shows that both the risk of the adverse events considered in this model, as well as the prevalence of T2D increases in older age groups (Chatterjee et al., 2017; DeFronzo et al., 2015; Lindbohm et al., 2019; Schmid, 2015). These probabilities and incidence rates need to be investigated in future research and incorporated in this microsimulation to allow for a more cohesive model of the natural disease history of patients.

A set of health outcomes, including quality of life, remission to normal glucose tolerance, and certain adverse events were considered in this model to capture the impact of a T2D prevention programme in a comprehensive way. A lifestyle intervention targeting dietary patterns and physical activity may, however, have much broader impacts on individual outcomes than displayed in this model. Apart from T2D and cardiovascular diseases, lifestyle interventions may also affect areas such as cancers, bodily pain, and mental health (Saha et al., 2013). Effects on these outcomes require further research, but it is likely that the cost-effectiveness of the lifestyle intervention was underestimated if these health benefits were also to be included.

The generalizability of the model's results is another aspect to be considered. The current version of the model is based on data from the PLIS trial, and therefore, the findings cannot be directly extrapolated to the entire population. However, this initial exploratory analysis has revealed important insights into the impact of factors such as the duration of the treatment effect on the cost-effectiveness of the trial. The lack of robust data on these aspects highlights the need for further research to better understand the mechanisms of lifestyle interventions on individual behaviour and disease outcomes. Further developments of this initial model are possible by adapting the code provided in the appendix to the paper with new data from Germany or other contexts.

This model utilized HbA1c as the primary screening tool to identify patients at risk of developing T2D that are eligible for participating in the lifestyle intervention. The selection of HbA1c was driven by its cost-effectiveness and ease of implementation in large populations (Bennett et al., 2007). However, it is crucial to acknowledge that different screening tests identify different populations of patients at risk. Therefore, the choice of a specific screening

mechanism can significantly influence the outcomes of the model. Each screening method has its advantages and shortcomings, and careful consideration must be given to choosing the most appropriate screening mechanism based on the context and available resources (Gyberg et al., 2015; Hu et al., 2010). It is important to note that the patient populations selected by each screening method may vary and thus affect the outcomes of future cost-effectiveness analyses (Diabetes Prevention Program Research Group, 2015; Gillett et al., 2015). There is some evidence that treatment effects of lifestyle interventions differs depending on whether patients were detected by HbA1c measurements or and OGTT (Diabetes Prevention Program Research Group, 2015), which underlines the importance of further research to identify the screening test that is best qualified to select patients that benefit the most from these interventions.

Incorporating pre-screening methods, such as the German diabetes risk score, could potentially enhance the cost-effectiveness of the intervention by targeting patients who are more likely to benefit from it. Unfortunately, due to the unavailability of data, this step could not be included in the model. Future research should focus on collecting relevant data to enable the integration of additional pre-screening methods into the model. By optimizing the targeting of at-risk individuals, the prevention program can be further refined, leading to improved outcomes and resource allocation (Schiborn et al., 2022).

Another significant challenge in predicting the outcomes of the model lies in adherence to screening and lifestyle treatment. Factors influencing adherence to the lifestyle treatment, such as socioeconomic status, health literacy, and individual motivations, are complex and multifaceted (Alberti et al., 2007; Dunkley et al., 2014; Sami et al., 2017). Individuals that attend screening programmes and health check-ups are not identical with those who do not take up these offers, and research suggests that individuals that do not get screened tend to be of poorer health (Simmons et al., 2011). Unfortunately, this version of the model does not incorporate underlying characteristics that may influence patients' likelihood of being screened and treated. Future iterations should consider incorporating such characteristics to provide a more realistic representation of patient behaviour and its impact on the outcomes of the prevention program.

In the context of lifestyle interventions, in may also be relevant to consider the effect of the intervention during its implementation as compared to the long-term effects on health outcomes. This model estimates health effects by assuming that the lifestyle intervention programme prevents or delays the onset of T2D and reduces the incidence of diabetes-

associated adverse events, which adds QALYs to a patient's lifespan. There is some evidence that lifestyle interventions also improve utility during the active intervention period measured by the EQ-5D, which could be described as a treatment effect that is independent of the preventive effect in the long run (Saha et al., 2013). This effect needs to be considered when comparing models such as the one used for this analysis to within-trial CEAs, since they measure different concepts of QALY gains.

5. Conclusion

This paper reports the development of a novel microsimulation state transition model to capture the costs and effects of a T2D prevention programme. It offers a structured approach to simulate effects on health outcomes and adverse events associated with T2D over a lifetime horizon. In contrast to many other models focused on lifestyle interventions targeting patients with prediabetes, this model also incorporated a screening campaign to identify patients at high risk of developing T2D, providing a more comprehensive picture of costs and effects. Despite the limitations imposed by data availability, this model offers valuable insights into the costs, utilities, and outcomes associated with various interventions. Future research should prioritize the collection of robust data to refine and expand the model, incorporating a broader range of factors and pre-screening methods. Additionally, understanding the impact of patient adherence and incorporating relevant patient characteristics will be crucial for accurately predicting the effectiveness and cost-effectiveness of the intervention. By addressing these limitations, further advancements can be made in the prevention of type 2 diabetes and the improvement of population health. Continued research efforts in the mechanisms underlying lifestyle interventions, the optimization of screening mechanisms, and the exploration of patient adherence patterns will contribute to the refinement and applicability of the microsimulation model in real-world settings.

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Verband Forschender Arzneimittelhersteller e.V. (2009). *Stellungnahme zum IQWiG-Methodenentwurf 1.0 zur Kosten-Nutzen-Bewertung*.

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World Health Organization. (2019). *Classification of diabetes mellitus*. World Health Organization. https://apps.who.int/iris/handle/10665/325182

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Appendix

A R Code

The following section contains the RMarkdown file used to populate and run the model. All functions are in a separate R code file, that is uploaded as a supplementary appendix to this thesis.

Introduction

This model was developed as part of the master thesis of Lisa Waltle in the programme "European Health Economics and Management (EuHEM) at the University of Oslo. It simulates individual patient level data to analyse costs and effects of a lifestyle intervention to prevent type 2 diabetes (T2D). The model incorporates a screening programme aimed at identifying individuals with prediabetes (PD), followed by a 2-year lifestyle intervention. Those diagnosed with PD are split up into a high and low risk group, as shown below. The lifestyle intervention is intensified in the high-risk group.

The lifestyle intervention and treatment effects used in this model are based on the Prediabetes Lifestyle Intervention Study (PLIS, DOI: 10.2337/db21-0526). Data sources for other background characteristics of the simulated patients, costs and adverse events are listed in the chapters below. The setting of this model is the German context, but can be adapted if needed.

The microsimulation Markov model consists of : normal glucose tolerance (NGT), detected prediabetes (PDud), diagnosed prediabetes in the high- and low-risk group, respectively (PDdLR) & PD(dHR), undetected T2D (T2Dud), diagnosed T2D (T2Dd) and death (D). Transition probabilities between the health states are a function of HbA1c levels. Mortality and the risk of adverse events are elevated in individuals with T2D.

01 Load packages

```
# load required packages

if (!require('pacman')) install.packages('pacman'); library(pacman)
# load (install if required) packages from CRAN
p_load('devtools', 'dplyr', 'scales', 'ellipse', 'ggplot2', 'lazyeval', 'i
graph', 'truncnorm', 'ggraph', 'reshape2', 'knitr', 'markdown', 'stringr',
'dampack', 'IPDfromKM', 'data.table')
# install_github('DARTH-git/darthtools', force = TRUE)
p_load_gh('DARTH-git/darthtools')
if(!require('truncnorm')) install.packages('truncnorm'); library(truncnorm
)
if(!require('expss')) install.packages('expss'); library(expss)
if(!require('readxl')) install.packages('readxl'); library (readxl)
```

02 Load functions

This function scripts currently holds all written functions that make this model work properly.

```
source("Functions_prediabetes_model.R")
```

03 Model input

03.1 Calculate population parameters based on samples in PLIS study

Source: Fritsche, A., Wagner, R., Heni, M., Kantartzis, K., Machann, J., Schick, F., Lehmann, R., Peter, A., Dannecker, C., Fritsche, L., Valenta, V., Schick, R., Nawroth, P. P., Kopf, S., Pfeiffer, A. F. H., Kabisch, S., Dambeck, U., Stumvoll, M., Blüher, M., … Häring, H.-U. (2021). Different Effects of Lifestyle Intervention in High- and Low-Risk Prediabetes: Results of the Randomized Controlled Prediabetes Lifestyle Intervention Study (PLIS). Diabetes, 70(12), 2785–2795. https://doi.org/10.2337/db21-0526

```
# calculate required parameters combining the high-risk and low-risk group
s in the PLIS study

n1 <- 124+77     # sample size of low-risk group
n2 <- 398+312    # sample size of high-risk group

### AGE
m1_age <- 57
m2_age <- 59
sd1_age <- 11
sd2_age <- 10
Mean_age <- ((n1 * m1_age) + (n2 * m2_age))/(n1 + n2)
SD_age <- sqrt(abs(((n1 - 1)*(sd1_age^2)+(n2-1)*(sd2_age^2)+((n1*n2)/(n1+n
2))*((m1_age^2)+(m2_age^2)-2*m1_age*m2_age))/(n1+n2-1)))

### BMI (Body-mass-index)
m1_bmi <- 28.1
m2_bmi <- 31.7
sd1_bmi <- 5.2
sd2_bmi <- 5.8
Mean_bmi <- ((n1 * m1_bmi) + (n2 * m2_bmi))/(n1 + n2)
SD_bmi <- sqrt(abs(((n1 - 1)*(sd1_bmi^2)+(n2-1)*(sd2_bmi^2)+((n1*n2)/(n1+n
2))*((m1_bmi^2)+(m2_bmi^2)-2*m1_bmi*m2_bmi))/(n1+n2-1)))

### PCG (Post-challenge glucose)
m1_pcg <- 6.8
m2_pcg <- 7.8
sd1_pcg <- 1.5
sd2_pcg <- 1.7
Mean_pcg <- ((n1 * m1_pcg) + (n2 * m2_pcg))/(n1 + n2)
SD_pcg <- sqrt(abs(((n1 - 1)*(sd1_pcg^2)+(n2-1)*(sd2_pcg^2)+((n1*n2)/(n1+n
2))*((m1_pcg^2)+(m2_pcg^2)-2*m1_pcg*m2_pcg))/(n1+n2-1)))

### HbA1c (Glycated haemoglobin A1c)
```

```
m1_hba1c <- 38.1
m2_hba1c <- 39.7
sd1_hba1c <- 3.6
sd2_hba1c <- 3.8
Mean_hba1c <- ((n1 * m1_hba1c) + (n2 * m2_hba1c))/(n1 + n2)
SD_hba1c <- sqrt(abs(((n1 - 1)*(sd1_hba1c^2)+(n2-1)*(sd2_hba1c^2)+((n1*n2)
/(n1+n2))*((m1_hba1c^2)+(m2_hba1c^2)-2*m1_hba1c*m2_hba1c))/(n1+n2-1)))

### LFC (Liver fat content)
m1_lfc <- 2.85
m2_lfc <- 10.45
sd1_lfc <- 2.29
sd2_lfc <- 8.19
Mean_lfc <- ((n1 * m1_lfc) + (n2 * m2_lfc))/(n1 + n2)
SD_lfc <- sqrt(abs(((n1 - 1)*(sd1_lfc^2)+(n2-1)*(sd2_lfc^2)+((n1*n2)/(n1+n
2))*((m1_lfc^2)+(m2_lfc^2)-2*m1_lfc*m2_lfc))/(n1+n2-1)))

### SMOK (Smoking status)

remove (m1_age, m1_bmi, m1_hba1c, m1_lfc, m1_pcg, m2_age, m2_bmi, m2_hba1c
, m2_lfc, m2_pcg, sd1_age, sd1_bmi, sd1_hba1c, sd1_lfc, sd2_age, sd2_bmi,
sd2_hba1c, sd2_lfc)
```

03.2 Load mortality rates for 2021 from external .xlsx file

Source: Statistischen Bundesamt, Todesursachen & Fortschreibung des Bevölkerungsstandes, https://www.destatis.de/DE/Home/_inhalt.html

```
# Mortality rates were already transformed to probabilities in the Excel f
ile
m.Mort <- read_excel("/Users/lisa2/Documents/0_STUDIUM/0_MASTER/THESIS/Mor
tality rates Germany.xlsx",
                sheet=1,
                range='A1:D661',
                col_names=TRUE)
```

03.3 Define model set-up

Sources: *Methodological guidelines, discounting:* Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. (2022). Allgemeine Methoden (Version 6.1). https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf

```
### General setup
n.i             <- 1000
# number of simulated individuals
n.t             <- 60
# time horizon, 60 cycles of 1 year each
v.n             <- c('NGT','PD(ud)','PD(dLR)','PD(dHR)','PD(dLRyr1)','PD(d
HRyr1)','T2D(ud)','T2D(d)','D')   # the model states
n.s             <- length(v.n)
# the number of health states
d.c <- d.e      <- 0.03
# discounting of costs and QALYs by 3%
```

```r
v.Trt           <- c("Standard of care", "Lifestyle intervention")
# store the strategy names
n.Trt           <- length(v.Trt)
# number of treatment strategies
v.Scr           <- c("No Screening", "Screening")
# screening strategies
n.Scr           <- length(v.Scr)
# number of screening strategies
n.sim           <- 100
# number of PSA simulations
v.names.cycles  <- paste("cycle", 0:n.t)
# cycle names
perspective     <- 1
# perspective of the analysis; 1 = societal, 0 = healthcare
```

04 Sample individual patient characteristics

04.1 Static characteristics

Sources: *Mean HbA1c for T2D:* Eeg-Olofsson, K., Cederholm, J., Nilsson, P. M., Zethelius, B., Svensson, A.-M., Gudbjörnsdóttir, S., & Eliasson, B. (2010). New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: An observational study from the Swedish National Diabetes Register (NDR). Journal of Internal Medicine, 268(5), 471–482. https://doi.org/10.1111/j.1365-2796.2010.02265.x; HbA1c is assumed to be higher for those with undiagnosed T2D than those with diagnosed (and managed) diabetes *Mean HbA1c for PD and NGT:* Tankova, T., Chakarova, N., Dakovska, L., & Atanassova, I. (2012). Assessment of HbA1c as a diagnostic tool in diabetes and prediabetes. Acta Diabetologica, 49(5), 371–378. https://doi.org/10.1007/s00592-011-0334-5 (could also be used for T2D)

```r
v.gender <- sample(0:1, n.i, replace = TRUE)
# 0 = male, 1 = female
v.age    <- rep(floor(Mean_age), times = n.i)
v.BMI    <- sample(rtruncnorm(n=n.i, a=25 , b=45,  mean=Mean_bmi, sd=SD_bm
i), n.i, replace = TRUE)
v.HbA1c  <- sample(rnorm(n.i, mean=Mean_hba1c, sd=SD_hba1c), n.i, replace
= TRUE)           # glycated hemoglobinA1c (mmol/mol)
v.LFC    <- sample(rtruncnorm(n=n.i, a=1, mean=Mean_lfc, sd=SD_lfc), n.i,
replace = TRUE)   # Liver fat content (%)
v.dur_T2D <- v.dur_PD <- rep(0, times = n.i)
# all patients start with no history of diagnosed (pre-)diabetes


# updated HbA1c values for patients that switch health states throughout t
he model
v.HbA1c_u_T2Dd <- sample(rtruncnorm(n=n.i, a=48, mean=50, sd=13.1), n.i, r
eplace = TRUE)            # updated HbA1c value (normally distributed in t
he diabetic range)
v.HbA1c_u_T2Dud <- sample(rtruncnorm(n=n.i, a=48, mean=60, sd=13.1), n.i,
replace = TRUE)           # updated HbA1c value (normally distributed in t
he diabetic range)
v.HbA1c_u_PD  <- sample(rtruncnorm(n=n.i, a=39, b = 47.999, mean=43, sd=9.
9), n.i, replace = TRUE)  # updated HbA1c value (normally distributed in t
```

```
he prediabetic range)
v.HbA1c_u_NGT <- sample(rtruncnorm(n=n.i, a=9, b = 38.999, mean=34, sd=7.1
), n.i, replace = TRUE)   # updated HbA1c value (normally distributed in t
he healthy range)

# Define HbA1c category to adjust TPs and make them individual-specific
v.HbA1c_TP_HR    <- ifelse (v.HbA1c < 31, 0.53, ifelse(v.HbA1c < 37, 1, if
else(v.HbA1c < 42, 1.8, 4.3)))
```

04.2 Dynamic characteristics

Variables included in this section will be updated over the individuals' lifetime in the model.

Probability of progression from NGT to PD and PD to T2D: Selvin, E., Steffes, M. W., Zhu, H., Matsushita, K., Wagenknecht, L., Pankow, J., Coresh, J., & Brancati, F. L. (2010). Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. The New England Journal of Medicine, 362(9), 800–811. https://doi.org/10.1056/NEJMoa0908359; data extracted with PlotDigitizer, 3.1.5, 2023, https://plotdigitizer.com DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., Hu, F. B., Kahn, C. R., Raz, I., Shulman, G. I., Simonson, D. C., Testa, M. A., & Weiss, R. (2015). Type 2 diabetes mellitus. Nature Reviews Disease Primers, 1(1), 15019. https://doi.org/10.1038/nrdp.2015.19

```
# diabetes status at baseline
v.status   <- ifelse(v.HbA1c >= 48, 1, ifelse(v.HbA1c >= 39, 2, 3))
# diabetes status at baseline
v.M_1      <- ifelse(v.status==1, "T2D(ud)", ifelse(v.status==2, "PD(ud)",
"NGT"))   # assign initial health state based on baseline diabetes status



# Treatment effect
v.TE_LR       <- sample(rtruncnorm(n=n.i, a=-0.9, b=0.2, mean=-0.5), n.i,
replace = TRUE)   # individual treatment effect in the LR group (conventio
nal lifestyle intervention)
v.TE_HR_conv  <- sample(rtruncnorm(n=n.i, a=-1.5, b=-0.7, mean=-1.0), n.i,
replace = TRUE)  # individual treatment effect in the HR group (convention
al lifestyle intervention)
v.TE_HR_int   <- sample(rtruncnorm(n=n.i, a=-1.8, b=-1.1, mean=-1.5), n.i,
replace = TRUE)  # individual treatment effect in the HR group (intensifie
d lifestyle intervention)

Screening       <- rep(0, n.i)       # nobody is being screened at baselin
e
screen_outcome  <- rep(0, n.i)       # nobody is being screened at baselin
e
HbA1c_baseline  <- rep(0, n.i)
return_fraction <- rep(0, n.i)
```

04.3 Create data frame with individual characteristics

```
## initialise a data frame with individual patient characteristics
df.i  <- data.frame(ID = 1:n.i,
                    M.init = v.M_1,
```

```
                    status = v.status,
                    gender = v.gender,
                    age = v.age,
                    BMI = v.BMI,
                    HbA1c = v.HbA1c,
                    LFC = v.LFC,
                    dur_PD = v.dur_PD,
                    dur_T2D = v.dur_T2D,
                    HbA1c_u_NGT = v.HbA1c_u_NGT,
                    HbA1c_u_PD = v.HbA1c_u_PD,
                    HbA1c_u_T2Dd = v.HbA1c_u_T2Dd,
                    HbA1c_u_T2Dud = v.HbA1c_u_T2Dud,
                    TE_LR = v.TE_LR,
                    TE_HR_conv = v.TE_HR_conv,
                    TE_HR_int = v.TE_HR_int,
                    HbA1c_TP_HR = v.HbA1c_TP_HR,
                    Screening = Screening,
                    screen_outcome = screen_outcome,
                    HbA1c_baseline = HbA1c_baseline,
                    return_fraction = return_fraction)
head(df.i)  # print the first rows of the data frame
```

05 Define model

05.1. Model input parameters

Sources: *Individual cost parameters:* Kassenärztliche Bundesvereinigung (KBV). Abrechnungsstatistik der Kassenärztlichen Bundesvereinigung: Honorarbericht nach §87c SGB V 1. Quartal 2013 bis 2. Quartal 2019 2020. https://www.kbv.de/html/honorarbericht.php; Verband der Privaten Krankenversicherung (PKV). Gebührenordnung für Ärzte (GOÄ): mit verkürzten Leistungsbezeichnungen- Kurz-GOÄ- 2013. https://www.derprivatpatient.de/sites/default/files/gebuehrenordnung-fuer-aerzte.pdf *Costs of T2D:* Ulrich, S., Holle, R., Wacker, M., Stark, R., Icks, A., Thorand, B., Peters, A., & Laxy, M. (2016). Cost burden of type 2 diabetes in Germany: Results from the population-based KORA studies. BMJ Open, 6(11), e012527. https://doi.org/10.1136/bmjopen-2016-012527 *Costs of PD:* 46% of costs of T2D (Ulrich et al. 2016), in line with Neumann, A., Lindholm, L., Norberg, M., Schoffer, O., Klug, S. J., & Norström, F. (2017). The cost-effectiveness of interventions targeting lifestyle change for the prevention of diabetes in a Swedish primary care and community based prevention program. The European Journal of Health Economics, 18(7), 905–919. https://doi.org/10.1007/s10198-016-0851-9 *Time costs for the intervention & participants' time cost:* Statistisches Bundesamt. (2021). Fachserie. 16, Verdienste und Arbeitskosten. Reihe 2, [Arbeitnehmerverdienste in Industrie und Handel]. 3, Arbeitnehmerverdienste im produzierenden Gewerbe. [Jährlich]. https://www.statistischebibliothek.de/mir/receive/DESerie_mods_00000301 *Costs of MI, CHF, stroke and angina pectoris:* Schmid, T. (2015). Costs of treating cardiovascular events in Germany: A systematic literature review. Health Economics Review, 5(1), 27. https://doi.org/10.1186/s13561-015-0063-5 *Costs of foot ulcer, end-stage renal disease and blindness:* References Kähm, K., Laxy, M., Schneider, U., Rogowski, W. H., Lhachimi, S. K., & Holle, R. (2018). Health Care Costs Associated With Incident Complications in Patients With

Type 2 Diabetes in Germany. Diabetes Care, 41(5), 971–978. https://doi.org/10.2337/dc17-1763 *Utilities, disutilities of AEs:* Kahn, R., Alperin, P., Eddy, D., Borch-Johnsen, K., Buse, J., Feigelman, J., Gregg, E., Holman, R. R., Kirkman, M. S., Stern, M., Tuomilehto, J., & Wareham, N. J. (2010). Age at initiation and frequency of screening to detect type 2 diabetes: A cost-effectiveness analysis. The Lancet, 375(9723), 1365–1374. https://doi.org/10.1016/S0140-6736(09)62162-0 *Probability of progression from NGT to PD and PD to T2D:* Selvin, E., Steffes, M. W., Zhu, H., Matsushita, K., Wagenknecht, L., Pankow, J., Coresh, J., & Brancati, F. L. (2010). Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. The New England Journal of Medicine, 362(9), 800–811. https://doi.org/10.1056/NEJMoa0908359; data extracted with PlotDigitizer, 3.1.5, 2023, https://plotdigitizer.com *Probability of T2D and PD remission:* Karter, A. J., Nundy, S., Parker, M. M., Moffet, H. H., & Huang, E. S. (2014). Incidence of remission in adults with type 2 diabetes: The diabetes & aging study. Diabetes Care, 37(12), 3188–3195. https://doi.org/10.2337/dc14-0874 (assumed to be equal) *HR of progression to T2D and AEs based on HbA1c levels:* Selvin, E., Steffes, M. W., Zhu, H., Matsushita, K., Wagenknecht, L., Pankow, J., Coresh, J., & Brancati, F. L. (2010). Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. The New England Journal of Medicine, 362(9), 800–811. https://doi.org/10.1056/NEJMoa0908359 *Probability of random clinical discovery of T2D:* assumption of lead time of 6-7 years, based on Gillett, M., Brennan, A., Watson, P., Khunti, K., Davies, M., Mostafa, S., & Gray, L. J. (2015). The cost-effectiveness of testing strategies for type 2 diabetes: A modelling study. Health Technology Assessment (Winchester, England), 19(33), 1–80. https://doi.org/10.3310/hta19330 *Probabilities of AEs:* Luijks, H., Schermer, T., Bor, H., van Weel, C., Lagro-Janssen, T., Biermans, M., & de Grauw, W. (2012). Prevalence and incidence density rates of chronic comorbidity in type 2 diabetes patients: An exploratory cohort study. BMC Medicine, 10(1), 128. https://doi.org/10.1186/1741-7015-10-128 *Risk reduction for AEs for patients with PD:* Palmer, A. J., Roze, S., Valentine, W. J., Minshall, M. E., Foos, V., Lurati, F. M., Lammert, M., & Spinas, G. A. (2004). The CORE Diabetes Model: Projecting Long-term Clinical Outcomes, Costs and Costeffectiveness of Interventions in Diabetes Mellitus (Types 1 and 2) to Support Clinical and Reimbursement Decision-making. Current Medical Research and Opinion, 20(sup1), S5–S26. https://doi.org/10.1185/030079904X1980 *General information on health check-up:* https://www.bundesgesundheitsministerium.de/checkup.html *Participation rate health check-up:* https://www.gbe-bund.de/gbe/pkg_isgbe5.prc_menu_olap?p_uid=gast&p_aid=84800889&p_sprache=D&p_help=2&p_indnr=779&p_indsp=1067&p_ityp=H&p_fid= *Test sensitivity and specificity:* Bennett, C. M., Guo, M., & Dharmage, S. C. (2007). Hba(1c) as a screening tool for detection of Type 2 diabetes: A systematic review. Diabetic Medicine : A Journal of the British Diabetic Association, 24(4), 333–343. https://doi.org/10.1111/j.1464-5491.2007.02106.x; Hu, Y [Yaomin], Liu, W., Chen, Y., Zhang, M., Wang, L., Zhou, H., Wu, P., Teng, X., Dong, Y., Zhou, J. w., Xu, H., Zheng, J., Li, S., Tao, T., Hu, Y [Yumei], & Jia, Y. (2010). Combined use of fasting plasma glucose and glycated hemoglobin A1c in the screening of diabetes and impaired glucose tolerance. Acta Diabetologica, 47(3), 231–236. https://doi.org/10.1007/s00592-009-0143-2

All costs, which were obtained from sources that did not use 2021 as a basis were indexed to 2021 prices based on the harmonized consumer price index (https://www.destatis.de/DE/Themen/Wirtschaft/Preise/Verbraucherpreisindex/Publikationen/_publikationen-verbraucherpreisindex.html#_mkhzadggu).

```
### Cost parameters

c.NGT            <- 0
c.PD.d           <- 1731.53                  # direct costs of PD (46% o
f T2D)
c.PD.id          <- 2119.47                  # indirect costs of PD (46%
of T2D)
c.T2D.d          <- 3764.19                  # direct costs of T2D, incl
uding physician visits, hospitalization and rehabilitation (95% CI [3255.4
9;4353.75])
c.T2D.id         <- 4607.54                  # indirect costs of T2D, in
cluding sick leave and productivity costs (95% CI [3395.86;6251.57])
c.Screen_HbA1c   <- 4                        # excl. time costs, since s
creening is assumed to happen during health check-ups
c.OGTT           <- 13.56                    # applied if HbA1c indicate
s T2D
c.PCP            <- 64.61                    # cost for one patient cont
act at the PCP, applied for re-testing via OGTT
c.LFC            <- 256.46                   # cost of measuring liver f
at content
c.LI_control     <- 23.05 * 0.5              # cost of control group (pe
r year) - 0.5 hr councelling session with dietitian
c.LI_conv        <- 23.05 * 8                # cost of lifestyle interve
ntion (per year)
c.LI_int         <- 23.05 * 16               # cost of intensified lifes
tyle intervention (per year)
c.Time_control   <- 25.96 * 0.5              # participants' time costs
(per hour * hours of intervention) in control group
c.Time_conv      <- 25.96 * (8 + (3 * 52))   # participants' time costs
(per hour * hours of intervention) in conventional LI
c.Time_int       <- 25.96 * (16 + (6 * 52))  # participants' time costs
(per hour * hours of intervention) in intensified LI

c.Angina         <- 4919.36      # costs of (unstable) angina pectoris (a
cute phase)
c.CHF            <- 4979.72      # costs of congestive heart failure (per
year)
c.RDyr1          <- 33107.21     # costs of end-stage renal disease (with
in year of event)
c.RDyr2          <- 23945.70     # costs of end-stage renal disease (afte
r year 1)
c.FUyr1          <- 4395.27      # costs of foot ulcer (within year of ev
ent)
c.FUyr2          <- 4703.49      # costs of foot ulcer (follow-up year)
c.MI             <- 15853.36     # costs of myocardial infarction (within
first year of event)
c.Blindyr1       <- 5908.01      # costs of serious eye disease/blindness
(within year of event)
c.Blindyr2       <- 3528.41      # costs of serious eye disease/blindness
(after year 1)
c.Strokeyr1      <- 14699.38     # costs of stroke (within year of event,
all types of stroke)
c.Strokeyr2      <- 7063.41      # costs of stroke (after year 1, all typ
es of stroke)
```

```r
### Utilities and disutilities

u.NGT          <- 1
u.PD           <- 1
u.T2D          <- 0.965            # utility w/o complication
du.Screen      <- -0.01            # disutility of a positive screening tes
t, only applied in year 1 of diagnosis
du.Angina      <- -0.18            # disutility of angina
du.CHF         <- -0.2             # disutility of congestive heart failure
du.RD          <- -0.2             # disutility of end-stage renal disease
du.FU          <- -0.17            # disutility of foot ulcer
du.MI          <- -0.18            # disutility of myocardial infarction
du.Blind       <- -0.16            # disutility of serious eye disease/blin
dness
du.Stroke      <- -0.167           # disutility of stroke

### Transition probabilities
# transition probabilities between health states
p.PD_NGT       <- 0.0028
p.T2Dud_T2Dd   <- 0.167
p.T2D_PD       <- 0.0028
HR.T2D_D       <- 1.8              # increased mortality associated with T2
D (hazard ratio)

### probabilities of adverse events

p.Angina.T2D        <- 0.0150              # probability of angina pector
is with T2D
p.CHF.T2D           <- 0.0161              # probability of congestive he
art failure with T2D
p.RD.T2D            <- 0.0015              # probability of end-stage ren
al disease with T2D
p.FU.T2D            <- 0.0107              # probability of foot ulcer wi
th T2D
p.MI.T2D            <- 0.0096              # probability of myocardial in
farction with T2D
p.Blind.T2D         <- 0.0024              # probability of serious eye d
isease/blindness with T2D
p.Stroke.T2D        <- 0.0146              # probability of stroke with T
2D

p.Angina.PD         <- p.Angina.T2D * 0.9  # probability of angina pector
is with PD
p.CHF.PD            <- p.CHF.T2D * 0.84    # probability of congestive he
art failure with PD
p.RD.PD             <- p.RD.T2D * 0.63     # probability of end-stage ren
al disease with PD
p.FU.PD             <- p.FU.T2D * 0.63     # probability of foot ulcer wi
th PD
p.MI.PD             <- p.MI.T2D * 0.86     # probability of myocardial in
farction with PD
p.Blind.PD          <- p.Blind.T2D * 0.63  # probability of serious eye d
isease/blindness with PD
```

```
p.Stroke.PD         <- p.Stroke.T2D * 0.57  # probability of stroke with P
D


### Screening-associated parameters
screen_age      <- 35                   # starting age for screening
screen_bmi      <- 25                   # starting BMI for screening
screen_int      <- 3                    # screening interval in number of
cycles
HC_prob         <- 1                    # probability of attending a healt
h-check
test_sens_PD    <- 0.66                 # HbA1c blood test sensitivity of
detecting prediabetes
test_sens_T2D   <- 0.965                # combined test sensitivity of HbA
1c blood test and OGTT of detecting type 2 diabetes
test_spec       <- 0.82                 # HbA1c blood test specificity

### Treatment-associated parameters
treat_eff_dur   <- 60                   # assumption: treatment effect is
sustained for x cycles and then returns to baseline over x cycles (see bel
ow)
treat_return_dur<- 60                   # assumption: treatment effect ret
urns to baseline over x cycles
```

05.2 Create list of input probabilities, costs and utilities

```
# List of parameters used for the calculation of the base case scenario
parameter.list.BC <- list(

## costs
c.NGT             <- c.NGT,
c.PD.d            <- c.PD.d,
c.PD.id           <- c.PD.id,
c.T2D.d           <- c.T2D.d,
c.T2D.id          <- c.T2D.id,
c.Screen_HbA1c    <- c.Screen_HbA1c,
c.OGTT            <- c.OGTT,
c.PCP             <- c.PCP,
c.LFC             <- c.LFC,
c.LI_control      <- c.LI_control,
c.LI_conv         <- c.LI_conv,
c.LI_int          <- c.LI_int,
c.Time_control    <- c.Time_control,
c.Time_conv       <- c.Time_conv,
c.Time_int        <- c.Time_int,
c.Angina          <- c.Angina,
c.CHF             <- c.CHF,
c.RDyr1           <- c.RDyr1,
c.RDyr2           <- c.RDyr2,
c.FUyr1           <- c.FUyr1,
c.FUyr2           <- c.FUyr2,
c.MI              <- c.MI,
c.Blindyr1        <- c.Blindyr1,
c.Blindyr2        <- c.Blindyr2,
```

```
c.Strokeyr1      <- c.Strokeyr1,
c.Strokeyr2      <- c.Strokeyr2,

## utilities and disutilities
u.NGT            <- u.NGT,
u.PD             <- u.PD,
u.T2D            <- u.T2D,
du.Screen        <- du.Screen,
du.Angina        <- du.Angina,
du.CHF           <- du.CHF,
du.RD            <- du.RD,
du.FU            <- du.FU,
du.MI            <- du.MI,
du.Blind         <- du.Blind,
du.Stroke        <- du.Stroke,

## transition probabilities
p.PD_NGT         <- p.PD_NGT,
p.T2Dud_T2Dd     <- p.T2Dud_T2Dd,
p.T2D_PD         <- p.T2D_PD,
p.Angina.T2D     <- p.Angina.T2D,
p.CHF.T2D        <- p.CHF.T2D,
p.RD.T2D         <- p.RD.T2D,
p.FU.T2D         <- p.FU.T2D,
p.MI.T2D         <- p.MI.T2D,
p.Blind.T2D      <- p.Blind.T2D,
p.Stroke.T2D     <- p.Stroke.T2D,
p.Angina.PD      <- p.Angina.PD,
p.CHF.PD         <- p.CHF.PD,
p.RD.PD          <- p.RD.PD,
p.FU.PD          <- p.FU.PD,
p.MI.PD          <- p.MI.PD,
p.Blind.PD       <- p.Blind.PD,
p.Stroke.PD      <- p.Stroke.PD,

## screening-associated parameters
HC_prob          <- HC_prob,
test_sens_PD     <- test_sens_PD,
test_sens_T2D    <- test_sens_T2D,
test_spec        <- test_spec,

## treatment-associated parameters
treat_eff_dur    <- treat_eff_dur,
treat_return_dur <- treat_return_dur
)
```

06 Run the microsimulation

```
source("Functions_prediabetes_model.R")
model_outcomes  <- decision_model(l.parameters = parameter.list.BC)
outcomes.SoC    <- model_outcomes$outcomes$outcomes.SoC
outcomes.LI     <- model_outcomes$outcomes$outcomes.LI
```

07 Outcomes

07.1 Relevant (health-related) outcomes

```
return_to_NGT.LI      <- colSums(outcomes.LI$TS[,1:n.t] == "PD(ud)->NGT")
+ colSums(outcomes.LI$TS[,1:n.t] == "PD(dLR)->NGT") + colSums(outcomes.LI$
TS[,1:n.t] == "PD(dHR)->NGT") + colSums(outcomes.LI$TS[,1:n.t] == "PD(dLRy
r1)->NGT") + colSums(outcomes.LI$TS[,1:n.t] == "PD(dHRyr1)->NGT")
return_to_NGT.LI      <- sum(return_to_NGT.LI)

return_to_NGT.SoC     <- colSums(outcomes.SoC$TS[,1:n.t] == "PD(ud)->NGT")
+ colSums(outcomes.SoC$TS[,1:n.t] == "PD(dLR)->NGT") + colSums(outcomes.So
C$TS[,1:n.t] == "PD(dHR)->NGT") + colSums(outcomes.SoC$TS[,1:n.t] == "PD(d
LRyr1)->NGT") + colSums(outcomes.SoC$TS[,1:n.t] == "PD(dHRyr1)->NGT")
return_to_NGT.SoC     <- sum(return_to_NGT.SoC)

print (return_to_NGT.LI)
print (return_to_NGT.SoC)

AEs.LI     <- outcomes.LI$df.AEs
AEs.SoC    <- outcomes.SoC$df.AEs

print (AEs.LI)
print (AEs.SoC)
```

08 Validation

```
# Higher 1.5 times higher rate of return to NGT in PLIS trial during the 2
-year follow up
return_to_NGT.LI_val1      <- colSums(outcomes.LI$TS[,1:4] == "PD(ud)->NGT
") + colSums(outcomes.LI$TS[,1:4] == "PD(dLR)->NGT") + colSums(outcomes.LI
$TS[,1:4] == "PD(dHR)->NGT") + colSums(outcomes.LI$TS[,1:4] == "PD(dLRyr1)
->NGT") + colSums(outcomes.LI$TS[,1:4] == "PD(dHRyr1)->NGT")
return_to_NGT.LI_val       <- sum(return_to_NGT.LI_val1)

return_to_NGT.SoC_val1     <- colSums(outcomes.SoC$TS[,1:4] == "PD(ud)->NG
T") + colSums(outcomes.SoC$TS[,1:4] == "PD(dLR)->NGT") + colSums(outcomes.
SoC$TS[,1:4] == "PD(dHR)->NGT") + colSums(outcomes.SoC$TS[,1:4] == "PD(dLR
yr1)->NGT") + colSums(outcomes.SoC$TS[,1:4] == "PD(dHRyr1)->NGT")
return_to_NGT.SoC_val      <- sum(return_to_NGT.SoC_val1)

print (return_to_NGT.LI_val)
print (return_to_NGT.SoC_val)

# diabetes incidence rate without screening
T2D_incidence <- colSums(outcomes.LI$TS[,1:n.t] == "PD(ud)->T2D(d)") + col
Sums(outcomes.LI$TS[,1:n.t] == "PD(dLR)->T2D(d)") + colSums(outcomes.LI$TS
[,1:n.t] == "PD(dHR)->T2D(d)") + colSums(outcomes.LI$TS[,1:n.t] == "PD(dLR
yr1)->T2D(d)") + colSums(outcomes.LI$TS[,1:n.t] == "PD(dHRyr1)->T2D(d)")
T2D_incidence <- sum(T2D_incidence)
T2D_inc_rate  <- T2D_incidence/(n.i*n.t)

print(T2D_inc_rate)
```

09 Cost-effectiveness analysis

```
# store the mean costs (and the MCSE)of each strategy in a new variable C
(vector costs)
v.C   <- c(outcomes.SoC$tc_hat, outcomes.LI$tc_hat)
sd.C  <- c(sd(outcomes.SoC$tc), sd(outcomes.LI$tc)) / sqrt(n.i)
# store the mean QALYs (and the MCSE) of each strategy in a new variable E
(vector health outcomes)
v.E   <- c(outcomes.SoC$te_hat, outcomes.LI$te_hat)
sd.E  <- c(sd(outcomes.SoC$te), sd(outcomes.LI$te)) / sqrt(n.i)

delta.C    <- v.C[2] - v.C[1]                  # calculate incremental co
sts
delta.E    <- v.E[2] - v.E[1]                  # calculate incremental QA
LYs
sd.delta.E <- sd(outcomes.LI$te - outcomes.SoC$te) / sqrt(n.i) # Monte Car
lo Squared Error (MCSE) of incremental costs
sd.delta.C <- sd(outcomes.LI$tc - outcomes.SoC$tc) / sqrt(n.i) # Monte Car
lo Squared Error (MCSE) of incremental QALYs
ICER       <- delta.C / delta.E                    # calculate the ICER
results    <- c(delta.C, delta.E, ICER)         # store the values in a ne
w variable

# Create full incremental cost-effectiveness analysis table
table_micro <- data.frame(
  c(round(v.C, 0)),           # costs per arm
  c(round(v.E, 3)),           # health outcomes per arm
  c("", round(delta.C, 0)),  # incremental costs
  c("", round(delta.E, 3)),  # incremental QALYs
  c("", round(ICER, 0))   # ICER
)

rownames(table_micro) <- c("Standard of care", "Lifestyle intervention")
# name the rows
colnames(table_micro) <- c("Costs",  "QALYs", "Incremental Costs", "QALYs
Gained", "ICER") # name the columns
table_micro  # print the table
```

10 Probabilistic sensitivity analysis

10.1 Create distributions of all relevant parameters

```
parameter_distributions <- list(

### costs

c.PD.d_gamma           <- gamma_params(c.PD.d, calc_sd(c.PD.d)),
#Gamma parameters of direct costs of being in PD
c.PD.id_gamma          <- gamma_params(c.PD.id, calc_sd(c.PD.id)),
#Gamma parameters of indirect costs of being in PD
c.T2D.d_gamma          <- gamma_params(c.T2D.d, calc_sd(c.T2D.d)),
#Gamma parameters of direct costs of being in T2D
c.T2D.id_gamma         <- gamma_params(c.T2D.id, calc_sd(c.T2D.id)),
#Gamma parameters of indirect costs of being in T2D
```

```
c.Screen_HbA1c_gamma   <- gamma_params(c.Screen_HbA1c, calc_sd(c.Screen_Hb
A1c)),     #Gamma parameters of HbA1c tests for screening
c.OGTT_gamma           <- gamma_params(c.OGTT, calc_sd(c.OGTT)),
#Gamma parameters of OGTT for screening/confirmation of T2D
c.PCP_gamma            <- gamma_params(c.PCP, calc_sd(c.PCP)),
#Gamma parameters of a PCP visit for LFC measurement/LF
c.LI_control_gamma     <- gamma_params(c.LI_control, calc_sd(c.LI_control)
),         #Gamma parameters of the LI (control group)
c.LI_conv_gamma        <- gamma_params(c.LI_conv, calc_sd(c.LI_conv)),
#Gamma parameters of the LI (conventional)
c.LI_int_gamma         <- gamma_params(c.LI_int, calc_sd(c.LI_int)),
#Gamma parameters of the LI (intensified)
c.Time_control_gamma   <- gamma_params(c.Time_control, calc_sd(c.Time_cont
rol)),     #Gamma parameters of participants' time costs in the LI (contro
l)
c.Time_conv_gamma      <- gamma_params(c.Time_conv, calc_sd(c.Time_conv)),
#Gamma parameters of participants' time costs in the LI (conventional)
c.Time_int_gamma       <- gamma_params(c.Time_int, calc_sd(c.Time_int)),
#Gamma parameters of participants' time costs in the LI (intensified)
c.Angina_gamma         <- gamma_params(c.Angina, calc_sd(c.Angina)),
#Gamma parameters of Angina pectoris
c.CHF_gamma            <- gamma_params(c.CHF, calc_sd(c.CHF)),
#Gamma parameters of chronic heart failure
c.RDyr1_gamma          <- gamma_params(c.RDyr1, calc_sd(c.RDyr1)),
#Gamma parameters of end-stage renal disease
c.RDyr2_gamma          <- gamma_params(c.RDyr2, calc_sd(c.RDyr2)),
#Gamma parameters of end-stage renal disease
c.FUyr1_gamma          <- gamma_params(c.FUyr1, calc_sd(c.FUyr1)),
#Gamma parameters of foot ulcers
c.FUyr2_gamma          <- gamma_params(c.FUyr2, calc_sd(c.FUyr2)),
#Gamma parameters of foot ulcers
c.MI_gamma             <- gamma_params(c.MI, calc_sd(c.MI)),
#Gamma parameters of myocardial infarctions
c.Blindyr1_gamma       <- gamma_params(c.Blindyr1, calc_sd(c.Blindyr1)),
#Gamma parameters of blindness
c.Blindyr2_gamma       <- gamma_params(c.Blindyr2, calc_sd(c.Blindyr2)),
#Gamma parameters of blindess in following years
c.Strokeyr1_gamma      <- gamma_params(c.Strokeyr1, calc_sd(c.Strokeyr1)),
#Gamma parameters of strokes
c.Strokeyr2_gamma      <- gamma_params(c.Strokeyr2, calc_sd(c.Strokeyr2)),
#Gamma parameters of strokes in following years

### utilities and disutilities

u.NGT_beta             <- u.NGT,
u.PD_beta              <- beta_params(u.PD, calc_sd(u.PD)),
#Beta parameters for the utility of being in PD
u.T2D_beta             <- beta_params(u.T2D, calc_sd(u.T2D)),
#Beta parameters for the utility of being in PD
du.Screen_beta         <- beta_params(du.Screen, calc_sd(du.Screen)),
#Beta parameters for the disutility of being screened positive
du.Angina_beta         <- beta_params(du.Angina, calc_sd(du.Angina)),
#Beta parameters for the disutility of angina pectoris
du.CHF_beta            <- beta_params(du.CHF, calc_sd(du.CHF)),
```

```
#Beta parameters for the disutility of CHF
du.RD_beta              <- beta_params(du.RD, calc_sd(du.RD)),
#Beta parameters for the disutility of RD
du.FU_beta              <- beta_params(du.FU, calc_sd(du.FU)),
#Beta parameters for the disutility of FU
du.MI_beta              <- beta_params(du.MI, calc_sd(du.MI)),
#Beta parameters for the disutility of MI
du.Blind_beta           <- beta_params(du.Blind, calc_sd(du.Blind)),
#Beta parameters for the disutility of blindness
du.Stroke_beta          <- beta_params(du.Stroke, calc_sd(du.Stroke)),
#Beta parameters for the disutility of a stroke

### transition probabilities
p.PD_NGT_beta           <- beta_params(p.PD_NGT, calc_sd(p.PD_NGT)),
p.T2Dud_T2Dd_beta       <- beta_params(p.T2Dud_T2Dd, calc_sd(p.T2Dud_T2Dd))
,
p.T2D_PD_beta           <- beta_params(p.T2D_PD, calc_sd(p.T2D_PD)),

p.Angina.T2D_beta       <- beta_params(p.Angina.T2D, calc_sd(p.Angina.T2D))
,
p.CHF.T2D_beta          <- beta_params(p.CHF.T2D, calc_sd(p.CHF.T2D)),
p.RD.T2D_beta           <- beta_params(p.RD.T2D, calc_sd(p.RD.T2D)),
p.FU.T2D_beta           <- beta_params(p.FU.T2D, calc_sd(p.FU.T2D)),
p.MI.T2D_beta           <- beta_params(p.MI.T2D, calc_sd(p.MI.T2D)),
p.Blind.T2D_beta        <- beta_params(p.Blind.T2D, calc_sd(p.Blind.T2D)),
p.Stroke.T2D_beta       <- beta_params(p.Stroke.T2D, calc_sd(p.Stroke.T2D))
,
p.Angina.PD_beta        <- beta_params(p.Angina.PD, calc_sd(p.Angina.PD)),
p.CHF.PD_beta           <- beta_params(p.CHF.PD, calc_sd(p.CHF.PD)),
p.RD.PD_beta            <- beta_params(p.RD.PD, calc_sd(p.RD.PD)),
p.FU.PD_beta            <- beta_params(p.FU.PD, calc_sd(p.FU.PD)),
p.MI.PD_beta            <- beta_params(p.MI.PD, calc_sd(p.MI.PD)),
p.Blind.PD_beta         <- beta_params(p.Blind.PD, calc_sd(p.Blind.PD)),
p.Stroke.PD_beta        <- beta_params(p.Stroke.PD, calc_sd(p.Stroke.PD))

)
```

10.2 Model input for PSA

```
# Store the parameter names into a vector
v.parameter.names    <- names(parameter.list.BC)

## Test functions to generate CE outcomes and PSA dataset

# Generate PSA input dataset
df_psa_input     <- generate_psa_parameters (n.sim = n.sim)

# First six observations
head(df_psa_input)

### Histogram of parameters
ggplot(melt(df_psa_input, variable.name = "Parameter"), aes(x = value)) +
  facet_wrap(~Parameter, scales = "free") +
  geom_histogram(aes(y = ..density..)) +
```

```
  ylab("") +
  theme_bw(base_size = 6) +
  theme(axis.text = element_text(size = 2),
        axis.title.x = element_blank(),
        axis.title.y = element_blank(),
        axis.text.y  = element_blank(),
        axis.ticks.y = element_blank())

ggsave(file = "..psa_parameters_distribution.png")
```

10.3 Run PSA

```
# Initialize data.frames with PSA output
# data.frame of costs
df_c           <- as.data.frame(matrix(0,
                                nrow = n.sim,
                                ncol = n.Trt))

colnames(df_c) <- v.Trt
# data.frame of effectiveness
df_e           <- as.data.frame(matrix(0,
                                nrow = n.sim,
                                ncol = n.Trt))
colnames(df_e) <- v.Trt


# Conduct probabilistic sensitivity analysis
# Run Markov model on each parameter set of PSA input dataset

for (i in 1:n.sim) {
  l_psa_input               <- update_param_list(parameter.list.BC, df_ps
a_input[i,])


  # Outcomes
  psa_output  <- decision_model(l_psa_input)


  df_c[i, ]     <- psa_output$df.ce$cost
  df_e[i, ]     <- psa_output$df.ce$effect


}df
```

10.4 Visualize PSA results for CEA

```
### Create PSA object
l_psa <- make_psa_obj(cost          = df_c,
                      effectiveness = df_e,
                      parameters    = df_psa_input,
                      strategies    = v.Trt)

l_psa$strategies <- v.Trt
colnames(l_psa$effectiveness) <- v.Trt
colnames(l_psa$cost) <- v.Trt
```

```r
# Vector with willingness-to-pay (WTP) thresholds.
v_wtp <- seq(0, 300000, by = 2000)
```

10.4.1 Cost-Effectiveness Scatter plot

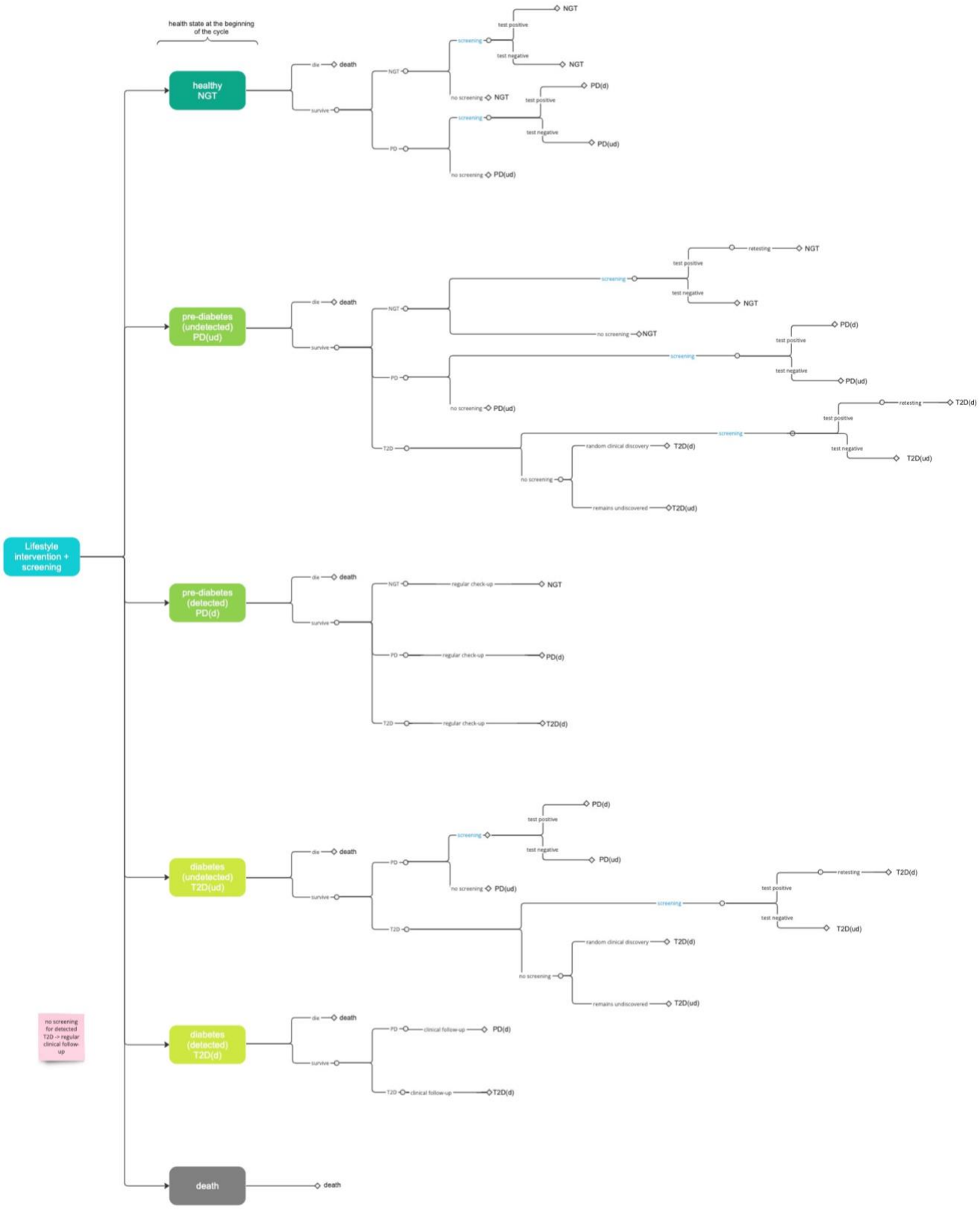
```r
### Cost-Effectiveness Scatter plot
txtsize <- 13
gg_scattter <- plot_psa(l_psa, txtsize = txtsize) +
  ggthemes::scale_color_colorblind() +
  ggthemes::scale_fill_colorblind() +
  scale_y_continuous("Cost (Thousand €)",
                     breaks = number_ticks(10),
                     labels = function(x) x/1000) +
  xlab("Effectiveness (QALYs)") +
  guides(col = guide_legend(nrow = 2)) +
  theme(legend.position = "bottom")
gg_scattter

ggsave(file = "..ce_scatterplot.png")
```

11.3.2 Incremental cost-effectiveness ratios (ICERs) with probabilistic output

```r
### Incremental cost-effectiveness ratios (ICERs) with probabilistic outpu
t
# Compute expected costs and effects for each strategy from the PSA
df_out_ce_psa <- summary(l_psa)
df_cea_psa    <- calculate_icers(cost       = df_out_ce_psa$meanCost,
                                 effect     = df_out_ce_psa$meanEffect,
                                 strategies = df_out_ce_psa$Strategy)
df_cea_psa
```

B Markov decision tree



C Input data tables

Table A1: Characteristics used to sample the patient population at the beginning of the model

	Distribution	*Mean**	*SD**	*Lower bound*	*Upper bound*
Age	uniform	58 [1]	0 [2]	58 [2]	58 [2]
Body mass index	truncated normal	30.91 [1]	5.86 [1]	25 [1]	45 [2]
HbA1c levels (mmol/mol)	normal	39.35 [1]	3.81 [1]		
Liver fat content (%)	truncated normal	8.77 [1]	7.96 [1]	1 [2]	

SD = standard deviation; * means and standard deviations were calculated to reflect the PLIS study population, i.e. both the high and low risk group

Data sources: [1] Fritsche et al. (2021), [2] assumption based on literature review

Table A2: Costs, probabilities and disutilities of diabetes-associated adverse events

	Duration	*Cost in year 1*	*Cost in following years*	*Disutility*	*Annual probability (T2D)*	*Relative risk with PD (compared to T2D)*
unstable angina pectoris	one-off	4919.36 [1]		-0.180 [3]	0.0150 [4]	0.90 [5]
coronary heart failure	chronic	4979.72 [1]		-0.200 [3]	0.0161 [4]	0.84 [5]
end-stage renal disease	chronic	33107.21 [2]	33107.21 [2]	-0.200 [3]	0.0015 [4]	0.63 [5]
foot ulcer	one-off	4395.27 [2]	4703.49 [2]	-0.170 [3]	0.0107 [4]	0.63 [5]
myocardial infarction	one-off	15853.36 [1]		-0.180 [3]	0.0096 [4]	0.86 [5]
blindness/serious eye disease	chronic	5908.01 [2]	3528.41 [2]	-0.160 [3]	0.0024 [4]	0.63 [5]
stroke	chronic	14699.38 [1]	7063.41 [1]	-0.167 [3]	0.0146 [4]	0.57 [5]

All cost parameters are obtained in Euro and have been indexed to 2021 using the German harmonized consumer price index (Deutsches Statistisches Bundesamt, n.d.)

Data sources: [1] Schmid et al. (2015), [2] Kähm et al. (2018) , [3] Kahn et al. (2010), [4] Luijks et al. (2012), [5] Palmer et al. (2004), [2] assumption based on literature review, [2] assumption based on literature review, [2] assumption based on literature review

Table A3: Cost parameters used for the microsimulation model in 2021 Euros			
	Parameter	*Assumptions & calculations*	*Data source*
Cost of being in normal glucose tolerance	0		[1]
Direct costs of prediabetes	1731.53	46% of direct costs of type 2 diabetes, in line with Neumann et al. (2017); direct costs include inpatient and outpatient care, medication, and rehabilitation	[1,2]
Indirect costs of prediabetes	2119.47	46% of indirect costs of type 2 diabetes, in line with Neumann et al. (2017); indirect costs include productivity losses, absence from work due to sickness or disability, and premature death	[1,2]
Direct costs of type 2 diabetes	3764.19	Direct costs include inpatient and outpatient care, medication, and rehabilitation	[2]
Indirect costs of type 2 diabetes	4607.54	Indirect costs include productivity losses, absence from work due to sickness or disability, and premature death	[2]
HbA1c screening tests	4.00	Only costs for the screening test were calculated, since it was assumed that this takes place during the regular health check-up, implying that no additional resources are used	[3,4]
Oral glucose tolerance test	13.56	For the confirmation of a type 2 diabetes diagnose in the HbA1c screening test, assumed to happen during a separate visit at the primary care provider	[3,4]
Primary care physician visit	64.61	Visit at the primary care provider to perform an oral glucose tolerance test or a liver fat content measurement	[3]
Liver fat content measurement	256.46	Liver fat content measurements are performed with a magnetic resonance spectroscopy. In the absence of price information for this procedure, the price of magnetic resonance tomography was used, since the procedures are based the same principles	[4]
Hourly cost for the intervention	23.05	Gross hourly wage of professionals (group 3) in the healthcare sector	[5]
Participants' time costs	25.96	Average gross hourly wage of employees in industry and retail; applied to both the time of the intervention and the recommended time for physical activity	[5]

All cost parameters are obtained in Euro and have been indexed to 2021 using the German harmonized consumer price index (Deutsches Statistisches Bundesamt, n.d.)
Data sources: [1] Neumann et al. (2017), [2] Ulrich et al. (2016), [3] Kassenärztliche Bundesvereinigung (2021), [4] Verband der Privaten Krankenversicherung (PKV) (2013), [5] Statistisches Bundesamt (2021a)

Table A4: Age-specific mortality rates for males and females in Germany

Age group	*Annual probability of dying for males*	*Annual probability of dying for females*
Under 1	0.33%	0.28%
1 to under 5	0.01%	0.01%
5 to under 10	0.01%	0.01%
10 to under 15	0.01%	0.01%
15 to under 20	0.03%	0.02%
20 to under 25	0.04%	0.02%
25 to under 30	0.05%	0.02%
30 to under 35	0.06%	0.03%
35 to under 40	0.10%	0.05%
40 to under 45	0.16%	0.09%
45 to under 50	0.26%	0.14%
50 to under 55	0.43%	0.23%
55 to under 60	0.73%	0.38%
60 to under 65	1.23%	0.63%
65 to under 70	1.95%	1.01%
70 to under 75	2.87%	1.59%
75 to under 80	4.43%	2.71%
80 to under 85	7.31%	4.88%
85 to under 90	13.36%	10.05%
90 and older	26.61%	23.25%

Data sources: Statistisches Bundesamt (2021b)
Mortality rates were transformed into transition probabilities based on Fleurence & Hollenbaek (2007)

Table A5: Boundaries for the distribution of updated HbA1c values (in mmol/mol) for individuals transitioning to a new health state

	Distribution	*Mean*	*SD*	*Lower bound*	*Upper bound*
Normal glucose tolerance	truncated normal	34 [3]	7.1 [3]	9 [2]	38.99 [2]
Prediabetes	truncated normal	43 [3]	9.9 [3]	39 [2]	47.99 [2]
Undiagnosed T2D	truncated normal	60 [1]	13.1 [1]	48 [2]	
Diagnosed T2D	truncated normal	50 [1]	13.1 [1]	48 [2]	

T2D = type 2 diabetes, SD = standard deviation

Data sources: [1] Eeg-Olofsson et al. (2010), [2] World Health Organization (2019), [3] Tankova et al. (2012)

D Validation

Validation check	Description and result
Extreme value checks	Extreme values for cost, utility and probability parameters were used in the model to ensure the model behaves as expected. Results were in line with what was to be expected.
TPs sum to one	Transition probabilities in the model sum up to 1. In addition, the number of individuals in each state during each cycle sum to 10,000 which shows that transitions between health states work as intended.
Compare to PLIS	In the PLIS trial, participants in the intervention group had a 1.5 times higher remission rate compared to those in the control group after the two-year follow-up period (Fritsche et al., 2021). The results of our analysis show that after 3 years, which corresponds to the intervention period of one year and the follow-up period, the return to normal glucose tolerance is 1.46 times higher in the intervention group, which validates the outcomes of the model with its main data source.
T2D incidence rate	In the absence of screening, the annual type 2 incidence rate resulting from the model is 6.8%. This is in line with the estimations of T2D incidence rates for detected T2D in Germany (National Diabetes Surveillance at the Robert Koch Institute, 2019; Tamayo et al., 2016).

E Probabilistic sensitivity analysis (PSA)

In the probabilistic sensitivity analysis (PSA), 100 Monte Carlo simulations of the microsimulation model were performed using the base case scenario of the microsimulation model. Computational efforts required for the simulations required the population in the model to be reduced to 1000 individuals.

The distributions of parameters used for sensitivity analysis can be seen below. Costs and utility for individuals in normal glucose tolerance were kept constant at 0 and 1, respectively. The utility of prediabetes was varied uniformly between the utility values of T2D and NGT. Disutilities for adverse events were varied uniformly, with twice the mean disutility as a lower bound and 0 as an upper bound. This was necessary because the small values could not be displayed in a beta distribution in R.

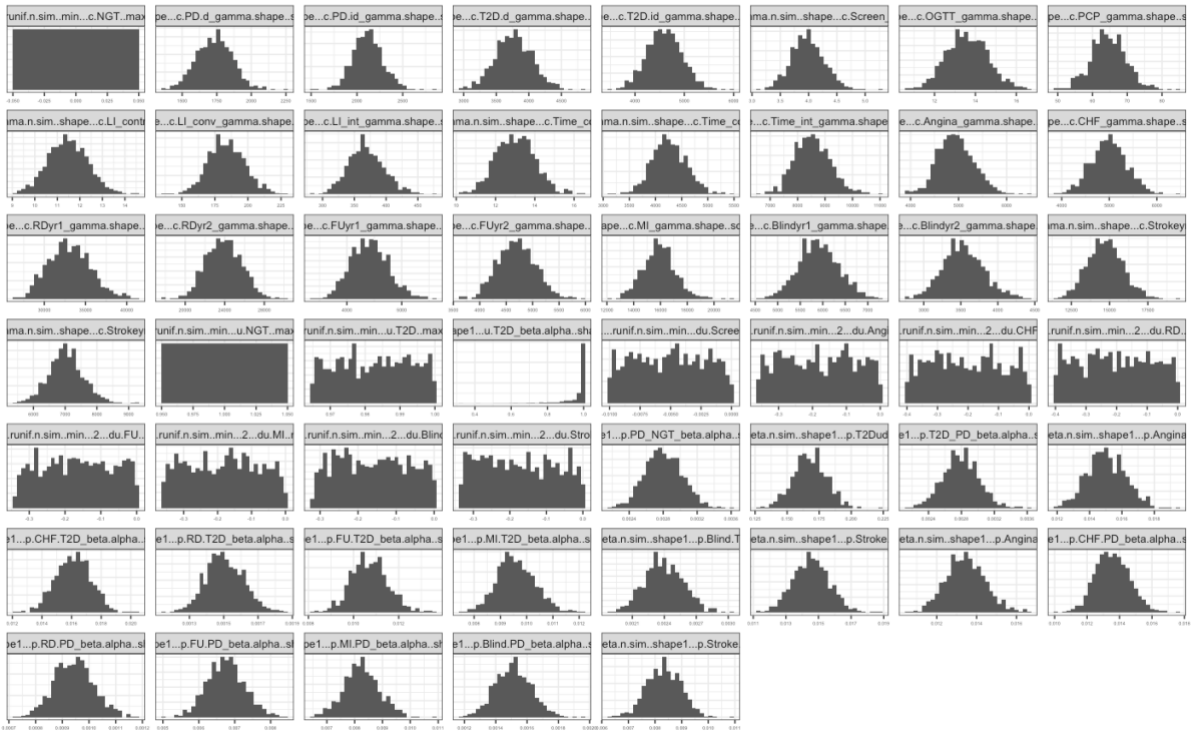


Figure 2: parameter distributions in the probabilistic sensitivity analysis

The results of the PSA are illustrated in the cost-effectiveness scatter plot below.

Cost (Thousand €)
112
110
108
106
104
102
100
98
96
94
92
90
88
25
25.02
25.04
25.06
25.08
25.1
25.12
25.14
25.16
Effectiveness (QALYs)
Strategy
Lifestyle intervention
Standard of care