Exploring opportunities to decrease the future healthcare burden of cardiovascular diseases

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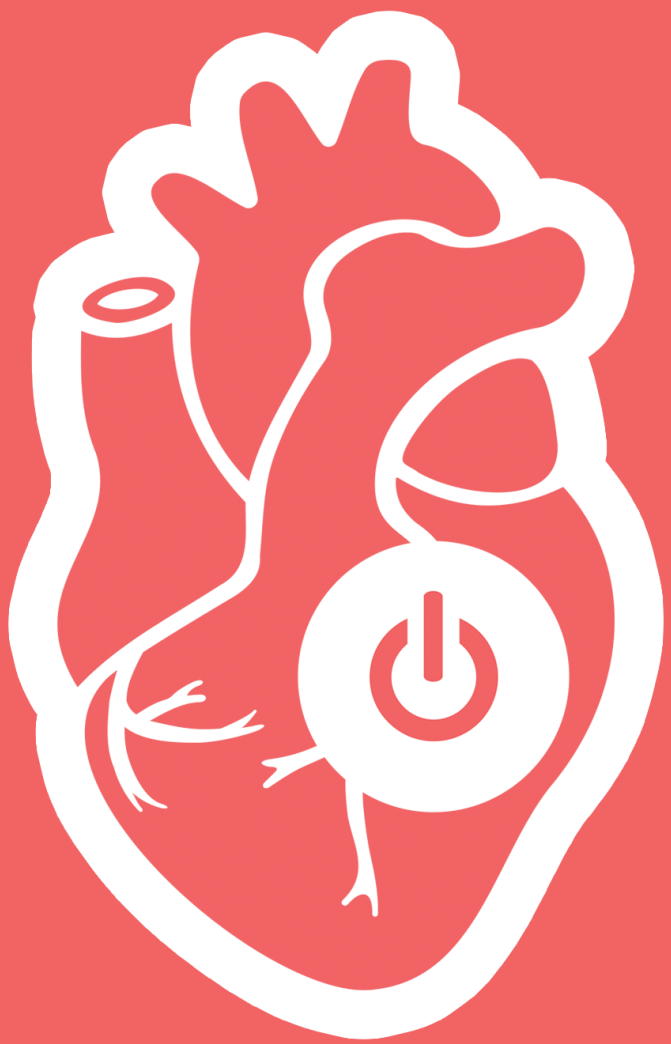

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Exploring opportunities to decrease the future healthcare burden of cardiovascular diseases

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Executive Summary

In the Netherlands, a substantial burden of morbidity and mortality persists for cardiovascular diseases in women. Despite this, the reduction of cardiovascular diseases in women has plateaued. This is against the backdrop of an ageing population and the prevalence of sedentary and unhealthy lifestyles.

This research presents a novel model to explore the problem space. A multi-disciplined microsimulation model is presented that incorporates theories and data aggregated from individual health data, population studies, social network studies, and behaviour studies. To our knowledge, it is the first model of its kind. We used the city of The Hague as our case study, as we were able to use a treasure trove of individual health data to inform the model, and thus inform the answer to the research question. The model was developed to answer the research question:

How can behavioural interventions decrease the healthcare burden of cardiovascular diseases among women in The Hague?

Our methodology consisted of multiple phases. First, we conducted a literature study to identify cardiovascular risk factors and entry points for interventions. Second, we developed health data models to be integrated into the microsimulation model. Third, we designed and implemented a microsimulation model and explored a plausible future cardiovascular health burden. Fourth, we looked at the impact of certain interventions applied to the entry points. The chosen interventions are based on the hypothesis that was derived from the literature read during the first phase. The hypothesis was as follows: *How can recurring interventions targeting diet, exercise or smoking behaviours decrease the healthcare burden of cardiovascular diseases among women in The Hague?*

During the literature study we conducted, we made multiple findings. First, current studies seem to omit relevant risk factors for women, such as pregnancy complications. So far, studies primarily focus on men, even though that cardiovascular diseases are the leading cause of morbidity and mortality for women in the world. Second, studies that examine risk factors oversimplify the nature of the problem and neglect cultural, social and even biological context. The problem is complex and multi-faceted. Thus, it warrants a fitting approach, such as the one presented in this research. Third, there is too little evidence on the efficacy of interventions targeting behaviours that lead to an increased risk of cardiovascular diseases.

During the development of the data models, we found that the cardiovascular risk of a young female is significantly higher if she has multiple risk factors – something that is currently not mentioned in the cardiovascular guidelines. We also found that smoking is the most dominant modifiable risk factor. However, since, in the model we developed, exercise and diet behaviour affect a woman's blood pressure, total cholesterol and blood sugar, indirectly, BMI may be just as, if not more, important. Our data model and our literature study thus confirm that these are important entry points that need to be exploited by interventions.

The simulation runs made the staggering revelation that, unless we do something about it, the future for women with regard to CVD looks bleak. The health issue is obstinate, and much of the prevention potential seems to be lost. The effects of many temperate interventions, such as education in schools, are negated, due to the oversaturation of unhealthy lifestyle behaviours. We also found that the effect of repeating interventions is more sustainable and long-term. However, our experiments implied that true progress can be made if extreme interventions are introduced repeatedly. Due to the intensity, it is unlikely the population of The Hague and additional stakeholders would approve of these interventions.

We nuance the findings by the fact that the model is a simplified representation of the real world. Choices were made during the design, and certain elements of human behaviour and of cardiovascular pathophysiology were omitted from the model. In some aspects, there simply was not enough data, such as on the effect of policies on a woman, but also how a woman is exactly influenced by her network and by external influences. These were some of the unknowns that could be addressed in future research.

This research concludes that there is an urgent need to introduce interventions that realise a sustainable, lasting change in the behaviours of women in The Hague. Three potential entry points are food intake, exercise, and smoking. Promoting healthier lifestyles is however only possible if we also address the social and cultural context. This model shows it is less effective to just change the behaviours of one woman, as social pressures may persuade her to fall back to her previous behaviours. We can set up women for success by involving her social network and as such decrease the barrier for her to permanently adopt a healthier lifestyle.

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1 Introduction

1.1. Societal relevance

To this day, cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality for women globally (Cho et al., 2020; Vogel et al., 2021). The overall reduction of CVD in women has stagnated in the past decade (Vogel et al., 2021). This is especially alarming considering that as much as 80% of CVD could be prevented or postponed if risk factors in lifestyle were to be eliminated (Piepoli et al., 2016).

Even though the mortality rates in the Netherlands have dropped in recent years, the absolute number of women with CVD has increased: currently, CVDs affect at least 0.75 million women in the Netherlands (de Boer et al., 2019; Nielen et al., n.d.). Projections show that the disease burden of CVDs will continue to rise until at least 2040 (Hilderink et al., 2020). This is explained by the fact that heart conditions are long-term conditions, as opposed to a short-lived episode, the ageing population, the unhealthier lifestyles people are adopting, and medical staff shortages (Batenburg et al., 2018; Centraal Bureau voor de Statistiek, 2022c).

A major adverse cardiovascular event (MACE) is a CVD event. It represents either a stroke or a myocardial infarction, lethal or non-lethal. A MACE often presents itself without symptoms (Balakumar et al., 2016; Cohn et al., 2003). This means there is a large number of morbidities and premature mortalities that can be prevented and as such the excessive disease burden of CVD. This is why Rose et al. (2008) suggest that a small reduction in risk in a large number of people may prevent more cases than treating a small number at high risk. This is the main argument to use population-level interventions, which is supported by a growing body of evidence (Capewell et al., 2010; Gupta & Wood, 2019; Unal et al., 2005).

However, interventions are complex and multi-faceted, so given the dire need for a solution, a real-time evaluation is not feasible, despite it being the norm in public health (Ramos Salas, 2015; Tracy et al., 2018). This is where simulation models come into play, as they can reveal the emerging properties of a population and reveal the effects of policies on them, often, in a matter of hours.

1.2. Prior work & Research Gap

There are a few discrepancies between men and women when it comes to the detection and management of CVDs. Despite the knowledge that women have unique physiology and experiences of illness, women have often been under-represented in, or even excluded from, clinical trials (Legato et al., 2016). Aside from biological differences, sociocultural differences, such as influence from the environment and nutritional and exercise habits, explain gender differences (Stramba-Badiale, 2010). These differences are currently often not incorporated in textbooks and guidelines (EUGenMed Cardiovascular Clinical Study Group et al., 2016; Gooding et al., 2020; Kouvari et al., 2018; Vynckier et al., 2022; Woodward, 2019).

At the population level, considerable risk reduction of future CVDs is achieved by improving prevention programmes focused on lifestyle modifications (Kotseva et al., 2020; van Trier et al., 2022). Programmes that address all aspects, including both pharmacological and non-pharmacological management, will not only reduce the burden of CVDs but also the burden of other diseases (Ermolao et al., 2019; Gajardo et al., 2020).

Similarly, by increasing screening efforts, we are more likely to identify women with an elevated risk and thus prevent negative consequences and/or disease progression (Duffy & Hameed, 2015;

European Society of Cardiology, 2021). This includes women who are asymptomatic and thus do not reach out to health professionals (de Waard et al., 2021). These women can then change their behaviours and modify their risk factors (Greenland et al., 2010).

In public health, it is quite common to use a 10-year risk score for the prediction of CVD events, such as the Framingham risk score and the SCORE models (Conroy, 2003; Kannel et al., 1976). Both only include a limited number of risk factors and exclude factors such as BMI. Additionally, it has been argued there should be more emphasis on lifetime risk as this is more relevant for people 50 years and older who may have a very high lifetime risk despite having a low 10-year risk (Berger et al., 2010).

A growing body of literature has shown that one's social network affects their health behaviours (Smith & Christakis, 2008). This notion has been included in models for obesity, but not for CVD (Ramirez-Nafarrate & Gutierrez-Garcia, 2013). Other social risk factors such as depression and factors such as birth complications have also been largely ignored (Chow et al., 2009; Harville et al., 2011; King, 1997).

Therefore, there is clear room for improvement regarding CVD prevention plans. There is also a demand, or rather a plea, for both public health interventions and clinical interventions to be grounded in science, theory, and data (Gooding et al., 2020). Simulation models are a logical consequence of this demand as they can account for both data and ethics and allow experimentation with (combinations) of interventions on a population *in silico* against a backdrop of uncertainty. Simulation models can incorporate the complexity and dynamic nature of populations, diseases, and interventions, allowing us to make sense of multiple pieces of evidence and interactions (Sterman, 2006). By synthesising and contextualising insights, data, and theories, the effect of interventions can be evaluated and compared (Freebairn et al., 2018).

Simulation models have been underutilised to gauge the effectiveness of CVD interventions. There are currently over 40 models exploring the public policy space with regard to CVDs (Unal et al., 2006). Most of these are Markov models or spreadsheet models (Breda et al., 2021; Lewsey et al., 2015; Saha et al., 2019; Salgado et al., 2019; World Health Organisation, 2019). As a result, these models are limited in their expressive power, as they are unable to account for interactions between agents and are unable to capture the heterogeneity within a population (Heeg et al., 2008; Standfield et al., 2014).

Concluding, there does not exist a holistic modelling approach to this public health issue. Up to our knowledge, existing models only take into account a small number of risk factors, do not look at the entire life cycle of a woman, ignore the influence of social circles, and ignore the fact that a vast number of people are asymptomatic despite having risk factors.

1.3. Scientific relevance

To evaluate intervention methods *in silico* a novel model was developed that looks at the entire life cycle of women and incorporated risk factors specific to women. To this end, paradigms from both decision-making under uncertainty and healthcare research were married. To be specific, the microsimulation model is an agent-based model that integrates both data models from healthcare and behavioural theories.

The model incorporates mechanisms to enable influences from vertical and horizontal relationships: vertical relationships refer to the relationships between women and their children, including genetic components, and horizontal relationships refer to the social circle of a woman.

Finally, the thesis makes a scientific contribution to the social discourse of data-driven decision-making in public healthcare. The problem is shrouded in uncertainty and complexity. To support decision making process and thus progress against the premature deaths caused by CVD, novel methods are needed to test interventions on the heterogeneous group of women at risk.

1.4. Problem statement and scope

This work addresses the excessive health burden of cardiovascular diseases for women. This research uses The Hague as a case study to generate a set of interventions that allow the reduction of risk factors in women. These can guide future investments into behavioural and/or screening interventions.

The Hague is characterised by its increasing diversity, segregation, and its increasing population density. The Hague is one of the most diverse cities in the Netherlands, despite the population being segregated when it comes to income and ethnic background (Boschman, 2012). This may be part

of the reason certain ethnic and socio-economic groups have a higher cardiovascular mortality rate compared to the Dutch (Kist et al., 2021).

The population of The Hague is ageing, and the city has faced and will continue to face medical staff shortages (Batenburg et al., 2018; Centraal Bureau voor de Statistiek, 2022c). These factors have and will continue to increase workload for medical staff, and will be reflected in the number of premature CVD mortalities that can be prevented.

1.5. Research question

Our overall objective is to get insights into how behavioural and screening interventions could be implemented to reduce the health burden of CVD in women while taking into account the shortcomings of previous guidelines and models. Hence, the main research question is as follows:

How can behavioural interventions decrease the healthcare burden of cardiovascular diseases among women in The Hague?

To ascertain the impacts of promising preventative screening and behavioural interventions, a microsimulation model was developed that exploits the knowledge that changes in lifestyle are effective in changing a woman's risk of a MACE. The data-driven model incorporates the high-level complexities inherent to CVD and the human body and allows us to explore the CVD intervention space over 50 years. This way, strategies can be tailor-made to fit the different demographic groups in the city to optimise effectiveness. They can be evaluated against each other and over time, allowing us to discern which interventions are short-term fixes and which can bring forth long-lasting change in the stage of The Hague.

1.6. Thesis structure

The thesis is organised into nine chapters. These chapters and their order have been described in Table 1.1. We want to emphasise that after the literature study, a hypothesis will be generated that will guide the remainder of the research.

Chapter	Description
1. Introduction	Presents problem definition, scope, background, aims, research question and gives an overview of the thesis.
2. Methodology	Lists the sub-questions and describes the methodology
3. Literature study	Presents the results of the literature study
4. Formalisaton	Presents the hypothesis inspired by the conducted literature study, describes the choice of model paradigm, and explains the design of the model
5. Experimental set-up	Presents the experimental setup based on the hypothesis
6. Implementation, validation and verification	Presents where the implementation can be found, and divulges on the validation and verification of the model
7. Simulation and data model results	Presents the results from one of the modules and the results from the simulations
8. Discussion	Discusses the results, the implications, insights and shows how the work relates to other studies.
9. Conclusion	Presents a syntehsis of key points and answers the sub-questions and research question

Table 1.1: An overview of all chapters and their contents. Appendices have been excluded

2 Methodology

This chapter describes the methods and approaches employed to answer the research question proposed in Section 1.5. Section 2.1 breaks down the overarching research question into sub-questions. The section after describes the research flow and the methods employed during all phases in the research flow.

Q	Method	Output	Data sources
SQ1	Literature study and expert consultation	Risk factors	Pubmed literature and health experts
SQ2	Literature study and expert consultation	Entry Points and hypothesis	Pubmed literature and and health experts
SQ3	Microsimulation	Model	SQ1 + SQ2 + hypothesis + additional data sources
SQ4	Microsimulation	Results of simulation of base case (and verification, validation, and sensitivity analysis)	SQ3
RQ	Microsimulation and synthesis	Results of simulation of interventions, discussion and conclusion	SQ1+SQ2+SQ3 +SQ4

Table 2.1: Alignment of sub-questions (Q) with methods and data sources.

Table 2.1 shows the alignment of the methods that are presented in this chapter with the sub-

questions and research question. Additionally it shows the input and output of each sub-question. The additional data sources mentioned in the input for SQ3 refer to input data necessary for the simulation model. The hypothesis that is generated when sub-question 2 is answered is used to guide the formalisation and the experimental set-up.

2.1. Sub-questions

To meet the objective the research question was dissected into four sub-questions. These sub-questions are, essentially, the framework of the thesis, as all methods have been selected to answer these questions.

Sub-question 1. What are the social and biological risk factors to reduce the health burden of CVD in women?

To find out how to decrease the healthcare burden of CVD, we need to know what factors determine the risk of getting a MACE. The factors that can be modified are of interest for health interventions. To get an idea of the full picture, we also need to explore the magnitude of all risk factors and look at the interplay between all of them. We will simplify the biological, social, and cultural elements of the system to form the base of the model that will be developed to answer the research question.

Sub-question 2. What are the entry points to reduce the health burden of CVD in women?

The end goal is to gauge the effectiveness of screening and behavioural interventions, so we need to know what kinds of entry points can be exploited by interventions. The entry points need to make sense contextually because if they do not, they are not sustainable: women are more likely to accept and vouch for interventions long-term if they match their worldview. The entry points also need to be logical, meaning that we target (part of) the root problem, and do not treat symptoms, and that, ideally, they affect multiple other risk factors positively.

Note that we are less interested in actual interventions. We found few studies explore the complex, long-term effects of interventions. Instead, we want to know what mechanism these interventions utilise.

Sub-question 3. How can health-related regression models be integrated into healthcare simulation modeling?

We need to combine multiple disciplines, such as computer science, social science, system science, and health science to evaluate the impact of CVD policies on women in the Hague. The findings from sub-questions 1 and 2 will be the basis of the model. We will develop a design that consolidates all relevant resources and that simplifies the complex health problem while remaining understandable. Its simplicity will enable a dialogue between all parties involved. McComb and Jablokow (2022) refer to this approach as generative multidisciplinarity: multiple disciplines are adapted to create a new discipline in its own right. In this specific case, that new discipline is health policy microsimulation.

Sub-question 4. What is a plausible future regarding cardiovascular diseases in women in the Hague in 50 years?

This sub-question looks at the simulation results of the model when the population is not subjected to intervention. Several scenarios will be explored to find out what trajectory the public health issue may take. Additionally, this sub-question allows for some validation. We can deliberate with field experts if their predictions align with the identified trajectories.

2.2. Research methods and research flow

This section describes the different methodologies applied to answer the sub-questions. First, we conducted a literature review to identify risk factors. The results of the literature review and the available data sources informed our modelling design decisions.

2.2.1. Literature review

To answer sub-question 1 we conducted a literature review on PubMed. We took an approach inspired by principles from systematic literature reviews to conduct this review rigorously. We used the search query shown in Figure 2.1in Pubmed. We only looked at literature published from 2012 to 2022, and only included meta-analyses, reviews, and systematic reviews. This was done due to time constraints.

Titles and abstracts were screened, after which we retrieved the full texts of potentially relevant articles. The full texts were read and categorised according to the risk factors that were addressed and emerging themes.

The literature review provided a jumping-off point but was not adequate to paint a full picture of the risk factors. To fill in the gaps, we followed up references and conducted targeted ad hoc review searches. This increased the number of references included in the review considerably, but did expose discrepancies between study findings, and, consequentially, allowed us to make better decisions regarding study design.

All sources were appraised based on usefulness and trustworthiness, including sample characteristics and study context. The appraisal was performed based on the following criteria: (1) the study needs to explore at least one risk factor of cardiovascular diseases; (2) The target group includes women; (3) full-length English or Dutch text needed to be available; (4) the authors need to be transparent regarding limitations and disclosures. The goal of this process was, on the one hand, to inform judgement about the strength of evidence for risk factors, and on the other hand to determine whether an article needed to be included. The main takeaways of all eligible sources are listed in section Chapter 3.

An overview of the process is shown in the PRISMA diagram provided in Figure 2.2.

```
("Diabetes Mellitus"[Mesh] OR diabetes[tiab] OR diabetic*[tiab] OR dm2[tiab]
OR niddm[tiab] OR dm 2[tiab] OR t2d[tiab] OR dm type 2[tiab] OR dm type
II[tiab] OR dm1[tiab] OR iddm[tiab] OR dm 1[tiab] OR t1d[tiab] OR dm type
1[tiab] OR dm type I[tiab] OR "blood glucose"[tiab] OR "blood sugar"[tiab]
OR "Hypertension"[Mesh] OR "Dyslipidemias"[Mesh] OR "Body Mass Index"[Mesh]
OR "Hypertension"[tiab] OR "High Blood Pressure"[tiab] OR "High Blood
Pressures"[tiab] OR "Dyslipidemia*"[tiab] OR "Dyslipoproteinemias"[tiab] OR
"Dyslipoproteinemia"[tiab] OR "Overweight"[Mesh] OR obese*[tiab] OR over-
weight*[tiab] OR obesit*[tiab] OR "body mass index"[tiab] OR bmi[tiab] OR
"Cholesterol"[Mesh] OR "cholesterol"[tiab]) AND ("Risk"[Majr] OR "Risk Fac-
tors"[Majr] OR "Risk Factor"[ti] OR "Risk Scores"[ti] OR "Risk Score"[ti])
AND ("Life Style"[Majr] OR "Health Behavior"[Majr] OR life style*[ti] OR
lifestyle*[ti] OR behavior*[ti] OR behaviour*[ti] OR "Smoking"[Majr] OR
"smoking"[ti] OR "Alcohol Drinking"[Majr] OR "alcohol consumption"[ti] OR
"diet*"[ti] OR "Exercise"[Majr] OR "physical activit*"[ti] OR "food"[ti] OR
"Diet, Food, and Nutrition"[Majr] OR "nutrition"[ti])
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Figure 2.1: Search query used in PubMed.

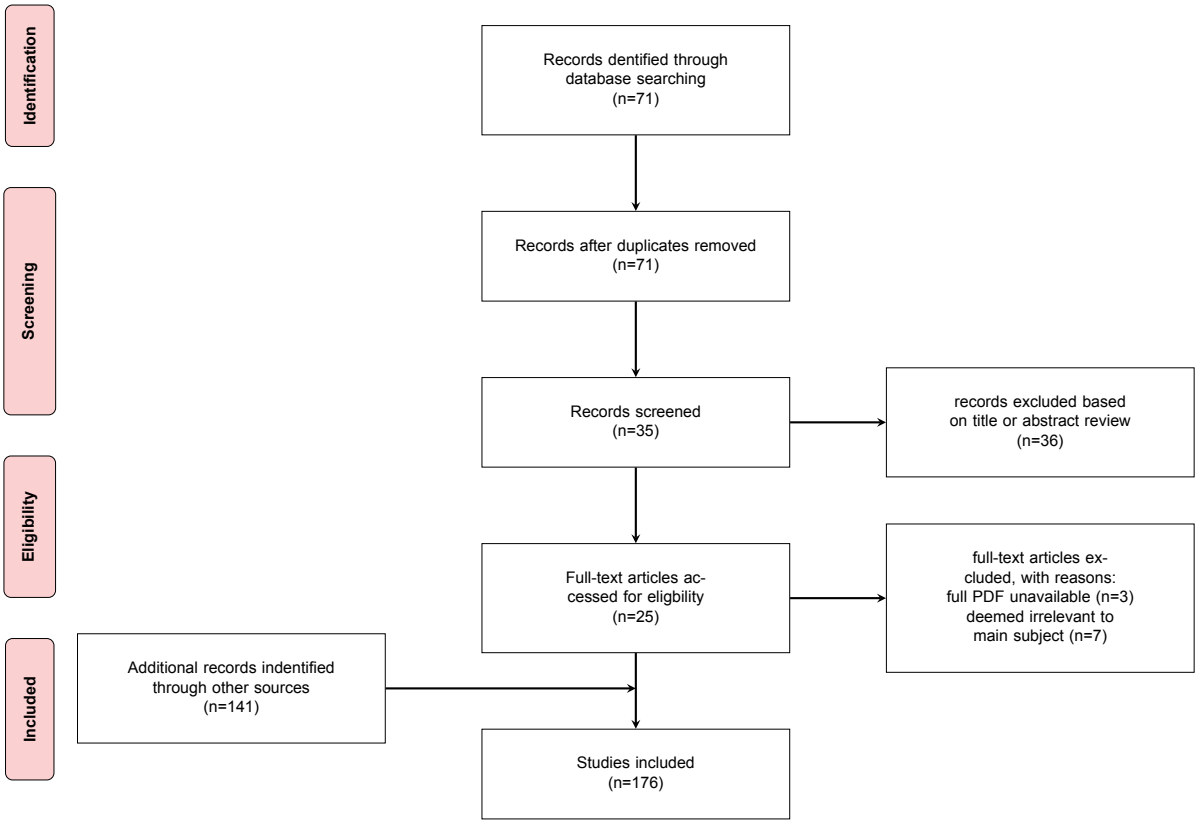

Figure 2.2: Systematic Literature review flow diagram

2.2.2. Hypothesis-driven simulation experiments

At the start of Chapter 4, a hypothesis will be generated that will be used as the foundation for both the simulation model and the experimental set-up. The reasoning for this is as follows: the model needs to accommodate the experiments which are based on the hypothesis. The choice for the modelling approach is described in Section 4.2.

The simulation model allows us to explore the effects of interventions on the entry points in silico without matching the real-time. The simulation model can simulate 50 years within a matter of hours. The model will show us the long-term effects, something we found missing from most studies (see Chapter 3.) We can vary the parameters of interventions exploiting the entry points identified for sub-question 2 to properly investigate the health issue.

To incorporate consistent and plausible pathways of the emergent behaviour of MACEs, uncertainties, intervention entry points, relationships and metrics were identified using an adapted version of the XLRM-framework (Lempert et al., 2003). The set X are uncertainties: factors outside of the control of the decision-makers, and in our specific case. In the original framework, the set L consists of policies that can potentially change the future of the population of the Hague. We have changed this set to be the entry points that can be exploited by interventions. In other words, we do not include concrete interventions, but we can explore how the system responds to outcomes of interventions. The reason for this is that there is simply too little data on specific policies. The set M includes all performance metrics that are used to value the performance of the interventions exploiting the intervention entry points. R signifies the links among the scenarios (X) and intervention entry points(L) as inputs or descriptors and the M, the performance metrics. The XLRM framework in Figure 2.3 is used to describe the modelling activities.

External uncertainties

This public health issue is subject to a lot of uncertainties. Some of these are inherent to the lack of knowledge, such as uncertainties about metabolic pathways, the interaction of genetic, hormonal, metabolic, and environmental factors, and the effect of lifestyle choices (EUGenMed Cardiovascular

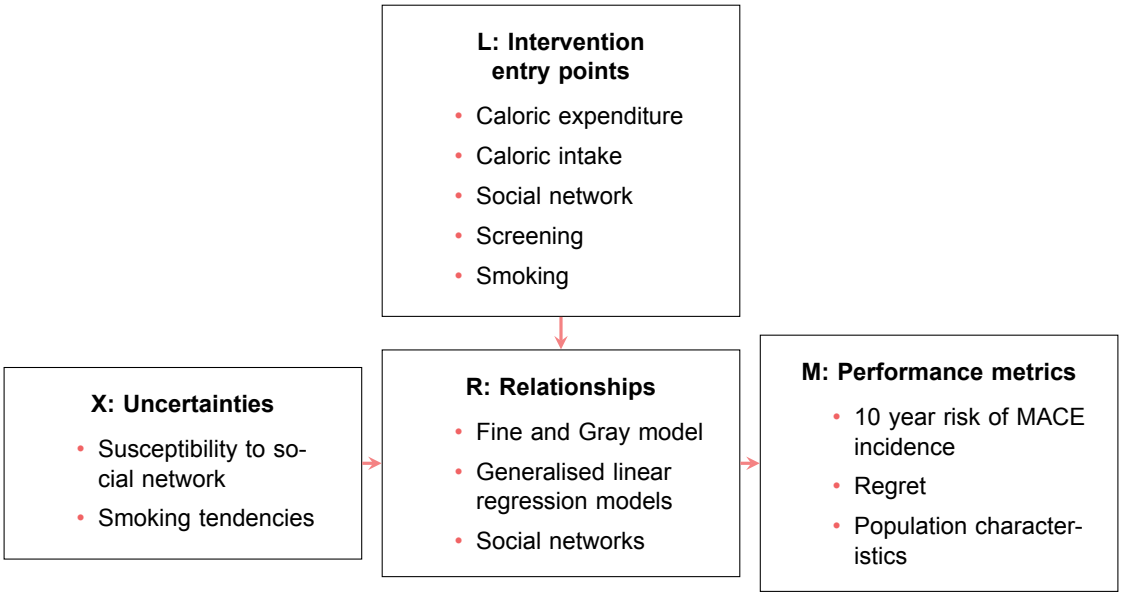

Figure 2.3: The XLRM model.

Clinical Study Group et al., 2016; Kouvari et al., 2018). However, these are internal uncertainties. This section concerns the external uncertainties, which are factors outside of a policy maker's control that influence both the course of CVD progression in the population and the effectiveness of policies.

To deal with external uncertainties, we made assumptions which have been described in in Chapter A and created scenarios. Most of these assumptions have been subjected to the sensitivity analysis described in Chapter 6 and Appendix B.

We opted to include two uncertainties that the real world has to face regardless. No study has been done on the susceptibility of women to their social circle. Similarly, we do not know how external factors will affect smoking behaviour of people in the Hague. These uncertainties were driven by expert opinion and literature. Note that we could have included many more scenarios, some of which have been discussed in the discussion.

Uncertainties in the form of external factors have been incorporated into scenarios. Different inputs passed on to the intervention entry points will be tested across the three scenarios that incorporate some of the uncertainties. The complete set of scenarios we developed for testing purposes is described in Chapter 5.

Intervention entry points

The research aims to discover the long-term implications of certain screening and behavioural interventions to decrease the healthcare burden of CVDs. These policies should aim to exploit strategic pathways to encourage dietary, lifestyle, and other behavioural changes in women. Lifestyle changes are shown to be effective in reducing the risk of CVDs (Gaziano et al., 2007).

In spite of the evidence, literature indicates that adherence to preventative strategies is subobtimal (Leung et al., 2017; Tibebu et al., 2017). It is argued that this is due to behavioural change being dependent on an individual's physical and social environment and the health care system (Berra, 2010). Considering this interplay, ideally, an intervention would be organised on the individual level.

However the population of the Hague is ageing, and there is a shortage in general practitioners (Centraal Bureau voor de Statistiek, 2021a; de Geit et al., 2022; Den Haag in Cijfers et al., 2021). Therefore it is infeasible to roll-out wide scale individual-level interventions. Instead, we are forced to be creative, set priorities, and use time effectively.

We have opted not to experiment with actual intervention strategies. Instead we use the results of possible policies. This means that multiple means may be able to have the same effect on the intervention entry point. Below, we listed the set L, the entry points our conceptual model will exploit. This set is based on the results from the literature study done in Chapter 3.

- caloric expenditure

Multiple strategies could be implemented to ensure the population of the Hague increases their exercise. Right now, the municipality of the Hague is focussing on offering sports that target certain age groups, and they are trying to ensure people in all neighbourhoods have equal opportunity to engage in sport activities (Municipality the Hague, 2015). Additionally, a budget is available for initiatives to ensure people in the Hague will exercise more regularly.

- caloric intake
  A reduction in caloric intake is a policy outcome that could be achieved nation-wide via a sugar-sweetened beverage tax (Colchero et al., 2017). The outcome could also be targeted at children by ensuring good quality school lunch programmes and curriculum-based education or adults via work-based interventions. Additionally, measures could be taken to reduce eating out and ordering food.

- social network
  As already shown in Section 3, most women are more likely to achieve or maintain weight loss if they are supported by friends, family, and coworkers. In fact, women also indicate that they would love for their progress to be monitored (Metzgar et al., 2015). External accountability is preferred by women.

- screening
  The monitoring frequency influences the number of women at risk that can be identified. Since general practitioners have access to a large segment of the population, they are in a favourable position to carry out certain preventative interventions. However, devices such as metabolic carts also show potential (Alcantara et al., 2022). They are not explicitly part of our research, but they are factors that enable certain interventionss.

- smoking
  The national government of the Netherlands aims to create a smoke-free generation in 2040 (Ministerie van Volksgezondheid, Welzijn en Sport, 2022). The Municipal Health Service is trying to support local organisations to achieve that goal by making the topic more addressable by the general public, while also trying to remove the smokers as much from view as possible (GGD Haaglanden, 2022). They argue that smoking is considered normal, as it is still quite visible in the municipality.

The actual interventions that use these entry points and the way they have been implemented are described in Chapter 5.

Performance metrics

The performance of the interventions will be measured with key performance indicators (KPIs). Three KPIs were selected to compare the intervention strategies.

The main KPI of interest are the results from the 10-year CVD risk model, which was trained on a large study of patients from The Hague. It was opted to use this method as opposed to the actual MACE probability, as it provides prognostic information and information about therapeutic strategies. A similar model is currently used in the Dutch Guideline Cardiovascular Risk Management (Nederlands Huisartsen Genootschap, 2019). The Guideline uses the SCORE-system (Conroy, 2003), which inspired the model that is described in Subsection 4.

CVD interventions may reduce the risk of chronic diseases that are not CVD while also alleviating the existing burden. In time, it may therefore decrease the workload of healthcare workers. Additionally, it will improve the quality of life of women, making them more productive members of society. For this reason we have opted to include population characteristics as a KPI.

Given that the public health issue is characterised by deep uncertainty, robustness is the final important criterion. A robust intervention strategy should perform decently across a wide range of plausible futures. This is also the reason for the emphasis on sensitivity analysis, as the results of the experiments are highly sensitive to assumptions. To accommodate robust decision-making (RDM), we introduce one additional KPI: regret (Lempert et al., 2006). Regret is defined as the difference between the performance of a strategy in a scenario and that of the best-performing strategy in that state. A robust strategy is therefore one with relatively small regret compared to alternatives across the range

of plausible futures. Regret of strategy s with $s \in S$ in state f with $f \in F$, is given in Equation 2.1 where strategy s' is the best performing strategy of all strategies in future state f.

$$Regret(s, f) = Max(Performance(s', f')) - Performance(s, f) \tag{2.1}$$

Relationships

The model is designed to evaluate the long-term consequences of alternative policy outcomes. This means we have to link the uncertainties, the interventions exploiting the intervention entry points and the KPI. This model is described in detail in Chapter 4. The order of operations is described in chapter 4. Besides parametric uncertainties, such as the effect of interventions, there are also some structural uncertainties. These uncertainties have been explained in Chapter A

Multiple data sources have been used to realise the relationships. They have been described in depth in Chapter 4. The model makes use of data from two private datasets, namely the Extramuraal LUMC Academisch Netwerk (ELAN) dataset and Centraal Bureau Statistiek (CBS) dataset (Leiden University Medical Center, n.d.). A high-level overview of the way the data models process the attributes of each female agent is shown in Figure 2.4. At initialisation all agents get attributes. During the run of the model, the attributes of the agents will change due to the influence of her social circle and external factors. Note that the social network changes over time as well. These are then used to calculate the 10-year risk of the first-ever MACE, which is a KPI, but also something fed back into the model to determine if an agent gets a MACE.

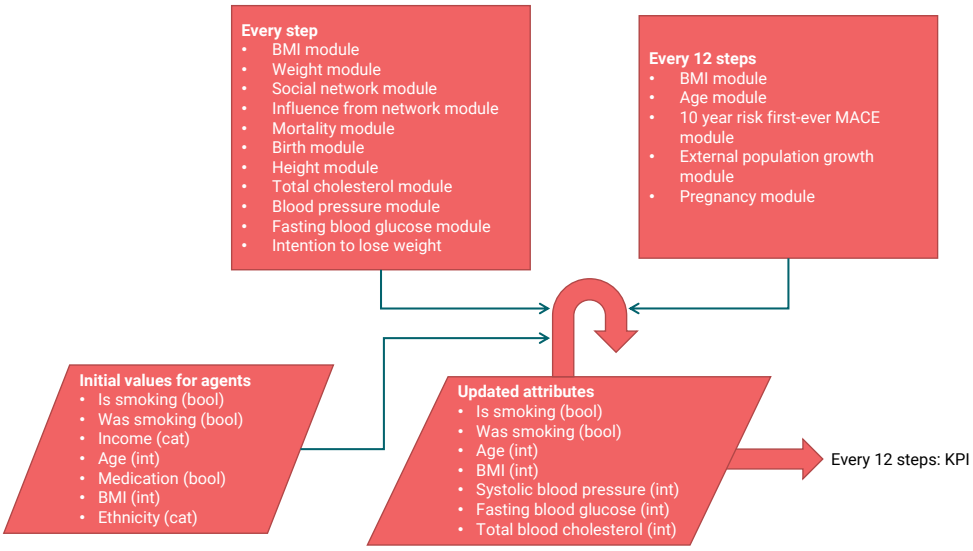

Figure 2.4: High-level overview of the model.

3

Literature study

In this chapter we present the results of the literature study that is described in Section 2.2.1. The goal of the literature study is to answer the two sub-questions: sub-question 1. What are the social and biological risk factors to reduce the health burden of CVD in women? and sub-question 2. What are the entry points to reduce the health burden of CVD in women? The objectives are to understand the risk factors for CVD, their interactions, and the interactions health interventions have on these risk factors. First, we explain the identified risk factors and how interventions have affected them, after which we show how they relate to each other. Then, we show the results from the literature study on the effect of social network on health behaviours. Finally, we wrap this chapter up with the answers to the two sub-questions.

In this section we categorised the risk factors between modifiable and non-modifiable risk-factors, but we would like to add the nuance that this classification is not strict. For instance, people can positively change their blood glucose values by making healthier life-choices, but they cannot reverse diabetes. Similarly, depression could be, arguably, placed in both categories. Someone who is depressed cannot just stop being depressed, but it is definitely just a phase for most women.

3.1. Modifiable risk factors

Studies suggest that 70%-90% of strokes are explained by modifiable risk factors (Prabhakaran & Chong, 2014; Yusuf et al., 2020). In theory, they are modifiable as they can be changed.

3.1.1. Medical

Hypertension, dyslipidaemia and diabetes are the most crucial medical modifiable risk factors contributing to CVDs (Vogel et al., 2021). These are considered the classical cardiometabolic risk biomarkers.

Lipid metabolism

Biomarkers in this category are cholesterol levels, their ratios, triglycerides and a few others (Hadgraft et al., 2021). Triglycerides store unused calories, whereas cholesterol is used as a building block for cells and certain hormones. Both contribute to fatty build-up in the arteries, which is called atherosclerosis, and may possibly be the mechanical reason of the correlation between the lipids and the risk of CVD (Kato, 2014). Unlike total cholesterol and low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol may reduce CVD risk as they carry LDL cholesterol away from the arteries to the liver, where LDL cholesterol is broken down.

Statins are the primary medication used to lower LDL cholesterol levels. LDL-cholesterol increases substantially during pregnancy, during which females should not be taking statins (Cifkova et al., 2019). Interestingly, lipid changes in women can be caused by hormonal changes and hormonal treatment (Cifkova et al., 2019). Finally, estrogen seems to slow down the progression of atherosclerosis (Winham et al., 2015).

Glucose metabolism

Biomarkers in this category include fasting glucose, fasting insulin, postprandial glucose/insulin and high-molecular weight adiponectin (HOMA) (Hadgraft et al., 2021). Most common used markers is the fasting blood glucose, although sometimes the fasting insulin level is used.

Multiple studies show that there is a positive association between fasting blood glucose (FPG) and CVD (Khan et al., 2014). The mechanistic pathways between the two is however unclear (Khan et al., 2014). One's FPG concentration is measured at least 8 hours after the last meal, and is ideally below 6.1 mmol/L. A rise in blood glucose levels causes insulin to be secreted, which is a hormone that helps converts glucose to glycogen for storage. When someone suffers from a FPG of 6.1 or above, they do not make enough insulin or their body is unable to properly use the available insulin. As a consequence glucose stays in their blood. People with an FPG between 6.1 mmol/L and 6.9 mmol/L or above are considered prediabetic or diabetic respectively (Diabetes Fonds, n.d.). Both are well-established risk factors for CVD.

There are three types of diabetes. Type 1 diabetes is an auto-immune disease, and its diagnosis is unaffected by lifestyle choice (Diabetes Fonds, n.d.). However, type 2 diabetes can be developed at any age due to lifestyle choices and is the most common type. Finally, women can develop an often temporary form of diabetes during pregnancy. This is called gestational diabetes, which has been shown to correlate with an increased risk to develop type 2 diabetes later on (Plows et al., 2018).

Traditionally, diabetes has been considered as a progressive, incurable condition. However, type 2 diabetes can go in remission, which means that the blood glucose levels revert back to the nondiabetic range (Gregg et al., 2012). Gestational diabetes is a temporary condition that occurs only during pregnancy.

There is an increase in type 2 diabetes in post-menopausal women as their insulin resistance increases (Cifkova et al., 2019). There is no consensus on the effects of breastfeeding on blood glucose levels, although not a lot of research has been done in this area (Owen et al., 2006).

Blood pressure

Some studies state that hypertension is the single most important modifiable risk factor (Kokubo, 2012; Prabhakaran & Chong, 2014). Blood pressure is generally assessed with resting blood pressure, which is typically reported separately as systolic and/or diastolic (Prabhakaran & Chong, 2014). When someone suffers from hypertension, the blood pressure is high enough that it narrows the arteries, which may lead to end organ damage (Schmieder, 2010). People can suffer from hypertension for years asymptomatically.

Hypertension and diabetes are interrelated: people with hypertension are more predisposed to develop diabetes, and hypertension is more common in diabetic females than females without (Mcfarlane et al., 2001; National High Blood Pressure Education Program Working Group on Primary Prevention of Hypertension, 1993). It is even claimed that up to 75% of CVD in diabetes may be attributable to hypertension (Sowers et al., 2001).

Exercise and diet has been shown to lower blood pressure (Hermansen, 2000). An increased sodium intake is associated with an increased change of getting hypertension and a CVD (S. Bhattacharya et al., 2022; Kokubo, 2012; Prabhakaran & Chong, 2014). Insufficient potassium or calcium in take has also been associated with an higher-than-average blood pressure and thus an increased risk of CVD (Hermansen, 2000; Kokubo, 2012).

Due to hormonal changes and life events, women are more inclined to develop a higher blood pressure (Cifkova et al., 2019). Hypertension is highly prevalent in post-menopausal women and oral contraception is associated with a small increase in blood pressure in most users and may actually induce overt hypertension (Cifkova et al., 2019).

Body anthropometry

Body anthropometry includes a wide range of measurements, such as BMI, waist circumference, other circumferences and body composition (total fat, total fat free or lean (Hadgraft et al., 2021). Most often reports use BMI and waist circumference as indicators (Ahmad et al., 2017)

Obesity is defined is a serious public health problem on its own, and its rising prevalence has been blamed on the easy access to high-fat foods and the tendency to over-eat (Andersen, 1999; Chen et al., 2021). It affects all other medical risk factors mentioned here.

Diet and physical activity both affect visceral adiposity, which is associated with insulin resistance and with an increased risk of developing a CVD (Carpenter et al., 2006). Because of the different sex hormones in men and women, adipose tissue is differently modulated (Carpenter et al., 2006). There may also be a genetic disposition (S. Li et al., 2010).

Systemic inflammation

Some studies reported on C reactive protein as a means to measure inflammation, but it was more often than not excluded (Hadgraft et al., 2021; Soare et al., 2014). Systemic inflammation is believed be (partly) caused by excessive caloric intake and physical inactivity (Boehncke, 2018; Soare et al., 2014). It has been theorised that inflammation participates in atherosclerosis (Libby, 2006), but the clear impact on risk of CVD is unclear due to a lack of data.

Obstructive sleep apnea

Obstructive sleep apnea is a condition that blocks part or all of the upper airway during sleep. It affects 35% of the Western adult population and is a known cardiovascular risk factor (Sidhu & Tang, 2017). Despite this it is underdiagnosed (Sidhu & Tang, 2017).

The relationship between obstructive sleep apnea and MACEs is however complex (Prabhakaran & Chong, 2014). It is argued it may change one's physiology, including blood pressure, cardiac structure, and atrial fibrillation. It may also be an independent risk factor.

3.1.2. Lifestyle

The targeted pharmacological treatment of the classical, medical risk factors mentioned above only treat part of the adverse consequences of unhealthy lifestyle habits. Bad lifestyle habits tend to affect more than just one medical risk factor. Instead of focusing on treating symptoms, the underlying causes could be sorted out as well. Self-management interventions have shown to have a significant effect on lifestyle risk factors (Sakakibara et al., 2017). This is especially true for medication adherence. Given that MACE prevention is highly influenced by lifestyle habits, women have a large degree of control in developing their own preventative habits.

Lifestyle changes should not include quick fixes such as intense, fast diet plans that promise dramatic results ("fad diets"), as they do not produce long-term results (Herriot et al., 2007). Interventions should promote robust and sustainable behaviour changes to reduce the risk of MACE.

Diet

It is well known that non-adherence to dietary guidelines is associated with an increased risk of CVD (Kjeldsen et al., 2022). Ge et al. (2020) observed that the kind of diet, such as low fat or low carbohydrate does not really affect cardiovascular risk factors.In other words, the composition of one's diet is less important than the caloric intake (Lassale et al., 2016; Soare et al., 2014).

Most studies show a positive association of the consumption of ultra-processed foods and medical risk factors (Silva Meneguelli et al., 2020). This is likely do to the fact that ultra-processed foods usually have a higher energy density and glycemic response compared to non-processed foods. They also do not tend to satisfy the consumer as long as non-processed foods, therefore increasing their consumption.

Recently, consumption of sugar-sweetened beverages has sky-rocketed (Avery et al., 2015). Studies have shown that a high intake of liquid calories does not reduce the intake of solid foods (Yu et al., 2018). There is also an increase in overconsumption, which may be due to increased overall stress, the accessibility of high-density food, and to the increase in eating out of home (Lachat et al., 2012; Wansink, 2014).

It is shown that younger people at risk tend to have worse dietary pattern than older people (Garshick et al., 2019). Women' s bodies tend to react differently than men's bodies to high-carbohydrate or high-fat diets. For instance, due to hormonal differences there is a a greater change in HDL cholesterol in women and thus diets have a less beneficial lipoprotein effect in women than in man (Knopp et al., 2005).

A lot of studies try to isolate certain elements from diet, such as certain vitamins, minerals, proteins, trans-fatty acids, and flavonoids (S. Bhattacharya et al., 2022; Fretts et al., 2015; Kokubo, 2012; Verneque et al., 2022; Vogtschmidt et al., 2021). Interestingly, multiple reports document what constitutes a healthy diet, but far less effort has been put into the behaviours leading up to dietary choices.

High concentrations of endocrine disrupting chemicals have been found in food items (Guzylack-Piriou & Ménard, 2021). Some of these can accumulate in tissues. A consequence of the disruption of the endocrine system is an interference with metabolism and behaviour, which may affect the likelihood of getting a MACE. It has also been hypothesised that pregnant women can predispose their fetuses

to obesity due to endocrine disrupting chemicals (Guzylack-Piriou & Ménard, 2021). Some, not all evidence, suggests these chemicals can induce gestational diabetes.

Finally, studies that looked at the effectiveness of both interventions explicitly trying to promote low-caloric foods, and interventions targeting nutritional value are inconclusive. Both low-caloric foods and healthy foods are related, making it unclear what approach is most effective biologically. Studies have shown the Dutch public is perceptive to these kinds of interventions, such as promoting lower-caloric, healthier products or increasing taxes of high-calorie products (An, 2013; Bos et al., 2013). However, there are no studies that look at long-term effectiveness and cost-effectiveness.

Physical activity

Exercise has been praised as a cost effective medication with a relatively low barrier (Byrnes & Buchholz, 2022). There are multiple benefits to physical activity. Not only will it increase the caloric expenditure, the body will also release dopamine. Additionally, exercise may make the person feel more empowered (Kagan & Morse, 1988).

Plenty of evidence show clear associations between physical activity and a reduced risk of developing CVD, type-2 diabetes and all-cause mortality (Garshick et al., 2019; Hadgraft et al., 2021; Lee et al., 2012; O'Keefe et al., 2021; Sallis et al., 2015; Saunders et al., 2014). This is true for normal-weight, overweight and obese individuals. People that meet the amount of exercise as recommended by guidelines have a significant reduced risk, whereas people with insufficient or excessive exercise do not (O'Keefe et al., 2021).

Sedentary lifestyle can negatively affect most, if not all, of the classical risk biomarkers (Hadgraft et al., 2021). People tend to eat more food when seated behind a screen (Saunders et al., 2014). Most studies seem to report on the link between increasing sedentary time and BMI (Ahmad et al., 2017).

Although it is relatively easy to start with physical activity, the challenge is sustaining it. It has been vouched physical activity should be incorporated in the daily routines of individuals (Sallis et al., 2015). All types of exercise seem to be beneficial (Byrnes & Buchholz, 2022; Chen et al., 2021), and the potential risks of exercise can be minimised by ensuring a proper approach (Sallis et al., 2015).

Many interventions have been tried to increase physical activity (Kahn et al., 2002). Some argue that more interventions should be directed at children, as their habits are being consolidated form childhood to adulthood (Ricotti et al., 2021).

Some studies show that the costs of physical inactivity are substantial (Sallis et al., 2015). However, these studies, just like the studies that try to show the effect of physical inactivity on non-communicable diseases, such as Lee et al. (2012), underline the difficulty of isolating "physical activity" from other risk factors.

Smoking

Smoking has been shown to be a well-established risk factor (Prabhakaran & Chong, 2014; Yuan et al., 2019). The SCORE risk chart implies that smoking amounts for about 50% of total CVD risk in women (Cifkova et al., 2019). Second-hand smoke may also be a plausible risk factor (Prabhakaran & Chong, 2014).

The literature does not agree on whether smoking is more harmful in women compared to men (Cifkova et al., 2019; Primatesta et al., 2001; Yuan et al., 2019). Smoking may cause more harm in women because women have an enhanced nicotine metabolism, particularly if they are using oral contraceptives, which affects platelet function and coagulation factors. The literature does show that women tend to smoke for social reasons opposed to being dependent on the drug (Carpenter et al., 2006).

Finally, smoking has the ability to diminish the healthy effect of other preventative measures (Kokubo, 2012). It is such an important risk factor, an additional cigarette outweighs the healthy effect of changes in other health behaviours.

Stress management

Stress is vaguely defined as "a state of threatened homeostatis provoked by a psychological, environmental or physiologic stressor" (Black & Garbutt, 2002). We found studies often used self-reportred values for stress to evaluate the value of stress on CVD and other risk factors. This is probably the reason why many studies contradict each other (Joynt et al., 2003). Some state stress is associated with a higher risk of MACE (Garshick et al., 2019), whereas other claim there is no association (Iso

et al., 2002). The same is true for the impact of stress on other risk factors and health behaviours. It is well-known stress is highly correlated with other risk factors, yet scientists cannot get on the same page regarding the actual correlation.

We could not find any public health intervention addressing stressors. We could however found a multitude of interventions introduced by business and educational organisations (Nilsen et al., 2006).

Alcohol consumption

Alcohol consumption, even as much as one drink, has been shown to increase the risk of MACE (O'Keefe et al., 2021). However, there are also studies that show a reduced risk of a first-ever MACE because of light to moderate alcohol consumption to both diabetes and CVD (Carlsson et al., 2005; Ronksley et al., 2011). It may be the case that everyone has a balance between of alcohol consumption and the risk of excessive use (and dependency), which needs to be weighed individually.

Current sttudies looking at interventions targeting alcohol consumption hardly ever apply a long-term follow-up time to provide conclusive answers on their effectiveness, and they also neglect ethical differences (Nilsen et al., 2006). This lack of breadth makes it hard to really assess the effectiveness of alcohol interventions.

Medication adherence

Medication adherence is defined as the process by which patients take their medications as prescribed. It includes the notion that prescriptions may change over time. The majority of young adults presenting with a myocardial infarction did not meet guideline-based criteria for prevention medications (Garshick et al., 2019). About half of the patients prescribed a preventative drug stops taking it within one year. (Vrijens et al., 2017; Zullig et al., 2015).

3.2. Non-modifiable risk factors

Non-modifiable risk factors cannot be changed. Interventions cannot affect them, but they are important for the big picture.

3.2.1. Age

Age is a major risk factor for CVD: the older you are, the higher your risk for CVD (Lakatta, 2002; Liberale et al., 2020). It is for this reason that most, if not all, CVD risk assessment tools are age-stratified. The hypothesised reason for this is that pathophysiological mechanisms change due to the ageing process. Differences between older and younger individuals have been extensively described (Lakatta, 2002). Older age is associated with less education, a higher BMI and lower physical activity, whereas middle-aged people have higher alcohol consumption (Schaakxs et al., 2017). Additionally, older people seem to be at a higher risk to develop type 2 diabetes and a high blood pressure (Kotchen et al., 1982; Laakso & Pyörälä, 1985).

3.2.2. Genetics

For nearly all of the disorders encompassed by CVD, inherited DNA sequences have been identified that indicate an increased risk for CVD (Kathiresan & Srivastava, 2012; Stephens & Humphries, 2003). Thus, this means that family history of early CVD is a risk factor (Imes & Lewis, 2014; Lloyd-Jones et al., 2004). Given that families tend to share common environments and other factors, the heredity and the unhealthy lifestyle can increase the risk of CVD even more.

Ethnicity, on its own, has largely been an ignored risk factor, but there are some studies suggesting it is a contributor (Gazzola et al., 2017; Winham et al., 2015). It is however unclear in these studies if this is truly caused by ethnicity, or by other lifestyle factors inherited from parents, making it, essentially, an epigenetic analysis.

3.2.3. Pregnancy

There are a couple of hypertensive disorders a women may suffer from during pregnancy: gestational hypertension, pre-eclampsia, eclampsia and diabetes. These conditions affect around 5-15% of pregnancies (Toloza et al., 2022; Vest & Cho, 2014).

Gestational hypertension and pre-eclampsia

Hypertensives disorders are common during pregnancy, affecting as least as 2-8% of pregnancies (Eiland et al., 2012). Women are diagnosed with pre-eclampsia if, aside from high blood pressure, they also suffer from kidney damage or damage to other organs during their pregnancy, which is indicated by proteinuria levels in their urine.

Women who have suffered from a hypertensive disorder during their pregnancy, have an increased risk of a CVD of 2.15% (Nederlandse Vereniging voor Obstetrie en Gynaecologie, 2014). Both gestational hypertension and pre-eclampsia are not just associated with an increased CVD risk, but also an increased risk of hypertension (Bellamy et al., 2007).

Gestational diabetes

In the Netherlands, there is a rise in gestational diabetes: it affected 7.5% pregnancies in 2019 opposed to the 5.1% of the pregnancies in 2015 (Horsselenberg et al., 2021). It is also clear that older females have a higher risk of gestational diabetes (Y. Li et al., 2020). Gestational diabetes is associated with a higher incidence of diabetes and CVD in later life (Bellamy et al., 2009).

3.2.4. Socioeconomic status

Socioeconomic status (SES) is usually assessed by occupation, education and income level. Data suggests that there exists a relationship between socioeconomic status and CVD (Kautzky-Willer et al., 2012; Kist et al., 2021). This may be due to a possible relationship between SES and quality of diet (Psaltopoulou et al., 2017). Spronk et al. (2014) show that the lack of nutrition knowledge contributes to poor dietary choices. This is especially true in regions and populations where access to education is limited (Cluss et al., 2013; Musaiger et al., 2013; Townsend et al., 2017).

It has also been shown that the biggest contributors to the risk of CVD differs per income group (Kist et al., 2021). The largest modifiable contributor in high income groups is smoking, hypertension and abdominal obesity. In mid income groups, the biggest 3 contributors are smoking, hypertension and education. In Low income groups all modifiable factors seem to have an amplified effect on their risk, and their poor diet is just as detrimental, if not more, than smoking (Yusuf et al., 2020).

3.2.5. Depression

Depression has been underdiagnosed in (future) cardiac patients for over 50 years, despite it being more common in patients with CVD than the general population (Hare et al., 2014). However, it is unclear to what extent depression affects the risk of a MACE in a person who has never had a MACE before. Some mechanisms of interactions have been proposed, but it is clear there are a lot of interactions with other risk factors, such as stress, which increases risk for both CVD and depression (Joynt et al., 2003).

Interventions targeting depression always deal with the symptoms after someone has received the diagnosis depression. They are never preventative, because those interventions address the other risk factors mentioned in this chapter (Jorm et al., 2000).

3.3. Effects from social network

A growing body of literature has shown that one's social network affects their health behaviours (Smith & Christakis, 2008): within social networks, diet and exercise behaviours are normalised or reinforced (Evans et al., 2016). Shepherd (1999) show that dietary choices are affected by the social context of a person. Multiple studies have shown that food choices are shared among family members (Feunekes et al., 1998), and that certain behaviours such as alcohol consumption, smoking, and snacking are transmissible in social networks (Pachucki et al., 2011). Christakis (2007) showed one is 57% more likely to become obese if they have a friend who has became obese. They also found similar increased risks among siblings and spouses. Interestingly, they observed that persons of the same sex had greater influence on each other than those of the opposite sex. They also conclude that geographic distance between two persons is less important than the quality of their relationship.

Metzgar et al. (2015) remark that women can identify social support as either a facilitator or a barrier. They show accountability to to others and support from friends, family members and coworkers are facilitators that allow women to maintain or continue weight loss following interventions. In the same vein, women reported that the lack of support was considered a barrier to achieve their weight loss

goals. Even more extreme, they report the social circle of a woman can also have an antagonistic nature, as they will tempt them with high-energy food. We also see this for other health behaviours, such as stress management. A woman may be more tolerable of high levels of stress if their social network is diverse (Nagy et al., 2022). The rationale for this is unclear: it may be, because the diversity influences her susceptibility for stressors, or because she has access to more diverse coping mechanisms and support through her support network.

Similarly, women have expressed that changes in physical activity conflicts with the need for social inclusion (Greaves et al., 2017): they expressed embarrassment around public exercising. Women have a desire to fit in, which is also the psychosocial argument for social eating (Janse Van Vuuren et al., 2015).

The rationale behind this is that that norms are often shared in social networks. Health behaviours and health outcomes can thus spread in social networks. There are a couple of mechanisms conceivable on the influence of social ties on a person's norms. The three most apparent ones are as follows: first, the person's perception on the acceptability of certain unhealthy and healthy behaviours can be altered; second, the network has a more direct impact and influences that person's food consumption and; third, it is a combination of the former two that affects a person's norms. Additionally, people within a network are exposed to common environmental factors, increasing the likelihood for all people in a network to adopt new lifestyle behaviours or outcomes at the same time.

Interestingly, our literature study also reveals that social relationships not only affect lifestyle behaviours, but that lifestyle behaviours may dictate one's social circle. It has been reported that there is a tendency for cluster formation of overweight and obese adolescents and adults (Evans et al., 2016). Other studies echo this sentiment: in at least the context of a school, people can be clustered according to BMI (Fletcher et al., 2011). This means we are not entirely sure of the causal pathways that lead to clusters: are people aware of their weight and compose their network accordingly, or does their network influence their behaviours? Maybe the actual truth lies in between these two extremes, after all, if one joins a gym, they are likely to befriend people that enjoy going to the gym. Likewise, if one becomes a smoker, they are more likely to befriend other smokers.

Multiple studies suggest that women with a spouse with diabetes are more likely to get diabetes themselves (Leong et al., 2014). There is an approximate two-fold risk increase for dysglycemia with spousal dysglycemia history. This shared diabetes risk in couples should inspire to couple-based interventions that take into account the collaboration between partners. This may also positively impact children, who are more likely to adopt behaviours from the mother than from the father (Hemminki et al., 2010; Karter et al., 1999; Scaglioni et al., 2018).

A woman's social network also affects other risk factors, such as alcohol consumption and smoking. The COVID-19 pandemic showed that alcohol consumption is, in general, a social behaviour, meaning that during confinement people will reduce their alcohol consumption frequency (Villanueva-Blasco et al., 2021). The observed nuance, however, is that some people resorted to alcohol consumption as a coping mechanism. So the exact intricacies of the effect of a woman's network on her alcohol consumption are still poorly understood. Similarly, smoking cessation by a spouse, decreases a woman's chances of smoking (Christakis, 2008).

Finally, women remark that self-accountability and self-monitoring was less important to them than external accountability (Metzgar et al., 2015). A likely hypothesis for this is that loved ones can affect the self control of a woman. Women will take into consideration the thoughts of others to assist them to achieve a goal, and the goal itself may be set because of their social relationships (Seeley & Gardner, 2006). Thus, social relationships pervade self accountability.

3.4. Interpretation

The initial literature study allowed us to gather a list of the risk factors that have been well-established and, slightly less established in literature. To aid interpretation, we also took a specific look at the interactions among the identified risk factors. The results are presented in Table 3.1. We have colored the origin blue of the relationships that have been included in the model described in Chapter 4. Note that the list is not extensive, for instance, the metabolic pathways of specific vitamins, such as vitamin D, and the influence of hormones are missing (Lind et al., 1995). The reason for this is the fact that these have been largely understudied, both theoretically and quantitatively, which is probably why they did not show up in our initial literature study. Similarly, we did not look at studies that inspect environmental risk

factors, such as a rural or urban environment. We also grouped stress and depression under “stress”, as their interactions with other risk factors are quite similar. Note that however both depression and stress can amplify each other. Additionally, we left out medication adherence is the influence of that factor is self-explanatory. Lastly, we simplified ”diet” to “caloric intake”, as we know we have enough data on caloric intake, but that the other components of diet as described in this section are too abstract or understudied to answer the research question.

As shown, there is a lot of interaction between the risk factors described in this chapter. That makes interpretation hard, as a lot of studies fail to acknowledge or control for these interactions. This may be one of the reasons why the studies prioritise different risk factors: everyone has a hard time dealing with the confounding effects, as risk factors amplify each other, and no true effort has been put into unravelling this mystery (Kokubo, 2012). Similarly, multiple health behaviours also have a combined effect.

The main take-away is that we lack lacking an understanding of the pathways and of the nature and extent of health improvements over longer periods. We have attempted to illustrate the relations we found in the literature study by creating a directed acyclic graph including all identified risk factors and effects. The graph is shown in Figure 3.1. All relationships were included. Note that the graph contains a cycle from BMI to depression to caloric intake to BMI again. The colours of the lines have no meaning: they are just there to make the graph more legible.

The dive into the literature also clearly shows that no interventions are a one-size-fits-all solution (Hadgraft et al., 2021). Some interventions are more effective in some populations but not others. Therefore, it makes sense to focus on policy outcomes as opposed to policies.

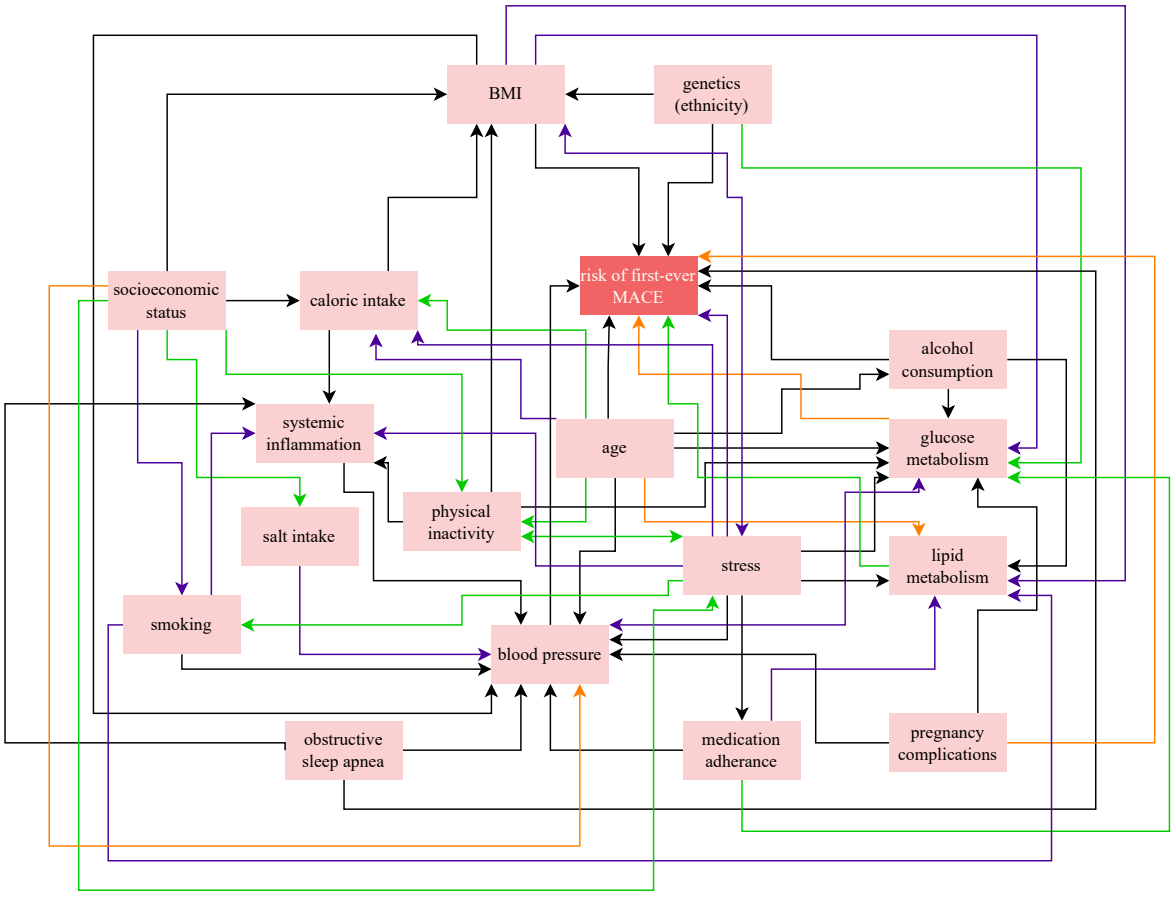

Figure 3.1: A directed acyclic graph showing the confounding effects of the identified risk factors.

Table 3.1: The effects the multiple risk factors have on each other and on the dependent variable: risk of first-ever MACE. The table concisely aims to show the directionality of the relationships and the reliability.

Origin	Destination	Effect	Reliability
alcohol consumption	risk of first-ever MACE	Alcohol consumption, even as much as one drink, has been shown to increase the risk of MACE (O'Keefe et al., 2021). However, there are also studies that show a reduced risk of a first-ever MACE because of light to moderate alcohol consumption to CVD (Carlsson et al., 2005; Ronksley et al., 2011).	Complicated and thus very nuanced, but established
alcohol consumption	lipid metabolism	The pathways are still unclear, but the correlation between the two has been well-established (Sozio & Crabb, 2008; You & Arteel, 2019).	Well-established risk factor, but poorly understood.
alcohol consumption	glucose metabolism	The relationship between alcohol and glucose metabolism is complicated, in some instances it will reduce the risk, whereas in other instances it will increase the risk of diabetes (Carlsson et al., 2005; Polsky & Akturk, 2017; Ronksley et al., 2011).	There seems to be an association, but understudied.
age	risk of first-ever MACE	There is a well-documented, positive relationship between age and risk of first-ever MACE (Chia et al., 2018; de Lucia et al., 2017; Nederlands Huisartsen Genootschap, 2019).	Well-established
age	alcohol consumption	Traditionally, for women, more so than men, age is an important predictor of the frequency of alcohol consumption (Mooney et al., 1987). However, Deeken et al. (2020) show that the relationship is far more complex, as it fluctuates across a woman's life, based on the different pressures she is subjected to and her susceptibility to them. They also argue there may be a genetic component, making people more prone to become addicted. Multiple studies try to dissect this relationship in more detail (Aguilar et al., 2022).	Complicated

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
age	glucose metabolism	Aging is by far the strongest known risk factor of diabetes (Chia et al., 2018). The relationship between age and glucose metabolism is complex (Chia et al., 2018). Diabetes is known to accelerate (biological) aging, and there has been some evidence that they share psychophysiological pathways. It is still unclear through what pathways this occurs, and a lot of other factors seem to intertwine with (biological) aging and hyperglycemia/diabetes.	Well-established correlation
age	lipid metabolism	Age is an established risk factor, but it is complicated by other risk factors and the complete biological picture is still unclear (Duntas & Brenta, 2018). Additionally, lipid metabolism plays a role in (biological) aging (Johnson & Stolzing, 2019).	Well-established risk factor
age	blood pressure	Studies have demonstrated over and over again that age is positively correlated with blood pressure (Taddei, 2009), however, opposed to the correlation of age with glucose and lipid metabolism, it may not be the most dominant risk factor (Lucas et al., 1985). The mechanisms are only partly known.	partial correlation
age	physical inactivity	In general, older age groups tend to exercise less than younger ones (Lind et al., 1995). This trend is especially clear when examining adults aged over 50 years (Watson et al., 2016). For younger age-groups, the relation is however complex due to other confounding factors. There is also some additional complexity, as physical inactivity and ageing both result in similar biological effects (Shur et al., 2021).	partial correlation
age	caloric intake	Alibhai (2005) and Sørbye et al. (2008) point out that it is common for elderly people to experience unintentional weight loss due to both caloric intake and several diseases and disorders.	Partial correlation

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
blood pressure	risk of first-ever MACE	It is well-documented that hypertension is one of the most important modifiable risk factors due to its strong association with CVD (Fuchs & Whelton, 2020; Kokubo, 2012; Prabhakaran & Chong, 2014).	Well established.
blood pressure	glucose metabolism	Hypertension and diabetes are interrelated: people with hypertension are more predisposed to develop diabetes, and hypertension is more common in diabetic females than females without (Mcfarlane et al., 2001; National High Blood Pressure Education Program Working Group on Primary Prevention of Hypertension, 1993). It is even claimed that up to 75% of CVD in diabetes may be attributable to hypertension (Sowers et al., 2001), but it's also been hypothesised that an increase in insulin resistance increases the chance of hypertension (Lucas et al., 1985; Matsuzawa et al., 1995; Reaven, 2003). Multiple mechanisms have been proposed for this (Lucas et al., 1985).	Poorly understood. Causal relationship remains a mystery. Possibly a two-way relationship.
BMI	stress	There is a correlation between BMI and stress/depression (Stunkard et al., 2003). Stunkard et al. (2003) hypothesise that there may be genetic predisposition for both depression and obesity, both may be affected by similar environmental factors, and/or both may affect each other.	Relationship is poorly understood, possibly due to its complexity, but there is a correlation. Possibly an (indirect) two-way relationship.
BMI	lipid metabolism	Lipid abnormalities are a known concomitant of obesity (Kannel et al., 1979).	Well-established.

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
BMI	glucose metabolism	There is a positive correlation between BMI and amount of substances that develop insulin resistance (Algoblan et al., 2014)	The relationship between the two is strong. There also seems to some superficial agreements on the pathogenesis between obesity and diabetes (Algoblan et al., 2014; Day & Bailey, 2011), but there still remains a lot unclear on details of the mechanisms (Kannel et al., 1979).
BMI	blood pressure	It is well known that obese persons have a higher likelihood of becoming hypertensive than nonobese persons. Weight gain, alone, can however not completely account for the rise in blood pressure (Lucas et al., 1985).	The relation between BMI and diastolic blood pressure is significant, however there is no consensus on the pathogenesis.
BMI	risk of first-ever MACE	It is clear that moderate-to-severe obesity takes a heavy toll on the cardiovascular system. It is also clear that the relation is complex and multi-faceted (Ortega et al., 2016).	The relationship is indisputable, however the relationship is far more complex than this.
caloric intake	BMI	There is a positive relationship between excessive caloric intake and risk of first-ever MACE. However, it needs to be said that this is only true if all other risk factors remain the same. Some studies vouch that it is more productive to increase energy expenditure opposed to reducing caloric intake (Fang et al., 2003; Lapidus et al., 1986).	Well-established.
caloric intake	systemic inflammation	There is a well-established relation between excessive calorie intake and systemic inflammation (Boehncke, 2018; Kökten et al., 2021; Soare et al., 2014). It is argued that many chronic diseases arise from diet-induced inflammation.	Growing body of evidence

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
genetics	BMI	There is some evidence to suggest that obesity can be inherited. Some loci have been identified that predispose women to obesity (Choquet & Meyre, 2011). Choquet and Meyre (2011) also show that gene identification can be used to learn more about the pathogenetic pathways	Only a portion of the genetic markers has been identified identified. As of now, it is unclear what the quantitative impact is of genetics on obesity.
genetics	glucose metabolism	The relation between genetics and type 1 diabetes is well established, but there also seem to be quite some loci that predispose people to type 2 diabetes (Vujkovic et al., 2020). Some of these loci are specific on the X chromosome.	We are finally starting to gain some insights in the relationship between genetics and the risk of type 2 diabetes, but there is still a lot of ground uncovered, There are a lot of obstacles obstructing the translation of genetic material to mechanistic pathways (Ingelsson & McCarthy, 2018).
glucose metabolism	risk of first-ever MACE	There is a positive association between fasting and non-fasting blood glucose and the risk of first-ever MACE (Chia et al., 2018; Cifkova et al., 2019).	Strong association
lipid metabolism	risk of first-ever MACE	Lipid biomarkers show a clear association with risk of first-ever MACE, even though the exact relation depends on the specific biomarker (Mc Auley & Mooney, 2014; Zhao et al., 2016). Other factors can interact with lipid metabolism, making it nearly impossible to isolate. Not all studies find the same relations between biomarkers and the risk of first-ever CVD, but the majority of studies confirm each others findings (Zhao et al., 2016).	Strong association
obstructive sleep apnea	blood pressure	Multiple, but not all studies show there is a postive relationship between obstructive sleep apnea and hypertension (Gonzaga et al., 2015), but the quantitative impact is still unclear.	Most evidence show a positive relation, but understudied.

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
obstructive sleep apnea	risk of first-ever MACE	The relationship between obstructive sleep apnea and risk of first-ever MACE is complex (Prabhakaran & Chong, 2014). It is argued it may change one's physiology, including blood pressure, inflammation, cardiac structure, and atrial fibrillation (Salman et al., 2020).	Poorly understood.
obstructive sleep apnea	systemic inflammation	Obstructive sleep apnea is a low-grade chronic inflammatory disease, and both will affect each other (Salman et al., 2020).	Poorly understood and two-way relationship.
physical activity	systemic inflammation	Systemic inflammation is believed be (partly) caused physical inactivity (Boehncke, 2018; Kökten et al., 2021; Soare et al., 2014).	Growing body of evidence
physical activity	stress	There may be a relationship between stress and physical activity, as some people use exercise to cope with stress, whereas others exercise less due to stress (Stults-Kolehmainen & Sinha, 2014).	Complicated and two-way.
physical activity	BMI	We are well aware of a relationship between physical activity and BMI (Wiklund, 2016). Currently, in the Netherlands, we see an increase in obesity while simultaneously also seeing a decline in daily energy expenditure. The relationship is however, complex, as physical activity may regulate food intake, which is a regulatory mechanism we have stopped exploiting due to our current sedentary lifestyles.	There is an association, but more research is needed regarding the mechanisms
pregnancy complications	blood pressure	Both gestational hypertension and pre-eclampsia are associated with an increased risk of hypertension (Bellamy et al., 2007). The association is significant (Wilson, 2003).	Significant
pregnancy complications	glucose metabolism	Gestational diabetes is associated with a higher incidence of diabetes in later life (Bellamy et al., 2009; McIntyre et al., 2019).	Well-established

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
pregnancy complications	risk of first-ever MACE	Women who have suffered from a hypertensive disorder, gestational diabetes or changes in lipid metabolism during their pregnancy, have an increased risk of CVD (Bellamy et al., 2009; Hubel, 2007; Nederlandse Vereniging voor Obstetrie en Gynaecologie, 2014; Valdiviezo et al., 2012). Note that however the proposed pathogeneses also include the relationship between pregnancy complications and other risk factors	Growing body of evidence, but, essentially an over-simplified association.
salt intake	blood pressure	Reports vary on the quantitative effect of salt intake on blood pressure (Cook, 2008; Lucas et al., 1985). Some authors do not find any relation at all (Robinson et al., 2019). It may also be the case that a woman's sensitivity to salt is very individual (Robinson et al., 2019).	Diverging conclusions.
smoking	systemic inflammation	Smoking acutely increases blood pressure, causes systemic inflammation and may cause atherosclerosis (Yanbaeva et al., 2007). Not all biological mechanisms are fully understood.	Well established correlation
smoking	blood pressure	The majority of studies show that chronic smokers have a slightly elevated blood pressure, whereas a small number do not show this association (Primatesta et al., 2001; Yanbaeva et al., 2007).	Somewhat accepted association, but not significant.
smoking	lipid metabolism	Multiple studies show that chronic smoking increases the risk of atherogenesis, and thus affects the lipid metabolism (Yanbaeva et al., 2007).	Association shown, but poorly understood.
socioeconomic status	stress	There is a well-established negative association between socioeconomic status and stres/depression (Miech & Shanahan, 2000; Nagy et al., 2022; Schaakxs et al., 2017). The hypothesis is that a low socioeconomic status can expose a woman to more stressors. Additionally, women with a higher socioeconomic status have access to more social resources to buffer against stress.	Well-established

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
socioeconomic status	BMI	A substantial number of studies show there exists a negative relationship between socioeconomic status and BMI im high-, middle- and low-income countries (Claassen et al., 2019; McLaren, 2007). It is hypothesised this is because of the environmental and psychological factors.	Well-established, but an oversimplified relationship.
socioeconomic status	salt intake	There seems to be a negative association between socioeconomic status and salt intake. A couple studies explored this relationship between regions within one country (Ji et al., 2013). All studies tried to, in their way, explain the relationship between socioeconomic status and blood pressure.	Understudied.
socioeconomic status	smoking	Whereas in the past, a high socioeconomic status was associated with an increased likelihood to smoke, currently this is true for groups with a low socio-economic status (Hiscock et al., 2012). There are however, a lot of nuances, and additional reasons why this is the case (reduced social support, lack of self-efficacy, marketing) (Hiscock et al., 2012).	Well-established inverse relationship, but mechanisms driving the relationship are unclear.
socioeconommic status	caloric intake	There seems to be a strong inverse relationship between socioeconomic status and caloric intake among women (Cheon & Hong, 2017; Sobal & Stunkard, 1989). It seems groups with a low socio-economic status have an increased appetite in general and prefer high-calorie foods.	Well-established.
socioeconomic status	physical exercise	Over the world, a higher socioeconomic status is asociated with more physical inactivity (Lind et al., 1995; Wister, 1996). However it is argued that this has less to do with income, and more with education and perceived barriers (Wister, 1996).	Established, but mechanisms are more hypothetical.

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
socioeconomic status	blood pressure	Most studies show there is a negative relationship (Grotto et al., 2008; Leng et al., 2015). Interestingly, a small number of studies contradict the relationship between socioeconomic status and salt intake, some studies observe a positive relationship between socioeconomic status and hypertension (Gilberts et al., 1994). This indicates that the relationship may be complex.	Unclear
stress	systemic inflammation	There is some evidence that indicates that stress can induce inflammatory changes (Cohen et al., 2015; Kim et al., 2022).	Some evidence, but pathophysiological processes are debatable.
stress	smoking	The relationship between stress and smoking is poorly understood, although some evidence indicates some women are more susceptible to changes in smoking status, if there are changes in stress levels (Cohen et al., 2015; Kassel et al., 2003)	Poorly understood and two-way.
stress	medication adherance	Stress has been associated with non-adherance to medication (Cohen et al., 2015; Kassel et al., 2003; Krousel-Wood et al., 2011).	Understudied, but indication of a positive relationship
stress	blood pressure	For years, it has been known psychological stress contributes to elevated blood pressure (“Associations between the Occupational Stress Index and Hypertension, Type 2 Diabetes Mellitus, and Lipid Disorders in Middle-Aged Men and Women”, 2012; Dressler, 1999)	Well-established
stress	lipid metabolism	Psychological stress has been associated with changes in lipid metabolism such as dyslipoidemia and atherosclerosis (“Associations between the Occupational Stress Index and Hypertension, Type 2 Diabetes Mellitus, and Lipid Disorders in Middle-Aged Men and Women”, 2012; Catalina-Romero et al., 2013; Gu et al., 2012).	Established, but pathways understudied.

Table 3.1 continued from previous page

Origin	Destination	Effect	Reliability
stress	glucose metabolism	Psychological stress has been associated with an increased risk of Type 2 Diabetes ("Associations between the Occupational Stress Index and Hypertension, Type 2 Diabetes Mellitus, and Lipid Disorders in Middle-Aged Men and Women", 2012; Hackett & Steptoe, 2017). There are multiple ways stress can cause the dysregulation of glucose metabolism, such as through inflammation, behaviours, and through hormones.	Established, but understudied.
stress	physical activity	Stress has been associated with both lower and higher levels of physical activity. Women may use exercise to cope with stress, whereas others exercise less due to stress (Cohen et al., 2015; Stults-Kolehmainen & Sinha, 2014).	Complicated and poorly understood
stress	caloric intake	Studies show that the release of stress hormones affects health behaviours, such as healthy food choices (Kim et al., 2022). Stress/ Depression may affect appetite both positively or negatively and thus affect caloric consumption (Fried & Nesse, 2015)	Complicated and thus unclear
stress	risk of first-ever MACE	Stress, whether caused by finances or personal reasons has been associated with a higher risk of MACE (Garshick et al., 2019).	This association exists, but it is probably oversimplified.
systemic inflammation	blood pressure	Systemic inflammation, which can be measured via different markers, may play a significant role in hypertension, however, although the relation is shown, it is vastly understudied (Bautista, 2003)	Indicative of an association, but understudied, the direction of the relationship is also not understood (Krishnan et al., 2014).

3.5. Conclusion

The literature study was conducted to answer two sub-questions. The first sub-question was as follows: sub-question 1: What are the social and biological risk factors to reduce the health burden of CVD in women?. We came across a multitude of interrelated risk-factors. Physiological changes that contribute to a woman's cardiovascular risk profile are multi-dimensional and they involve the interaction of multiple other risk factors and biological systems. Thus, we think that it is no longer appropriate to rely on the traditional risk factors to define CVD risk. It is also clear clear there is still a lot of research that needs to be done to understand the complexities.

To answer the second sub-question, sub-question 2. What are the entry points to reduce the health burden of CVD in women?, we identified multiple entry points. Most sources we found were regarding: energy expenditure, caloric intake, smoking and alcohol usage. We found less studies on medication adherance and stress/depression, but they may still prove to be useful. Finally, a potentially interesting entry point that has received the least attention is the nutritional composition of a woman's diet. If interventions target these behaviours we may be able to change the cardiovascular health trajectories of women.

4

Formalisation

This chapter describes the model in such a way that anyone can reproduce the model without looking at the source code. More information about the actual implementation of the model can be found in Chapter 6. The chapter is divided into three parts. In Section 4.2 we motivate why we opted to use agent-based modelling to tackle the CVD issue. Next, in Section 4.3, we provide an overview of the chronological steps that are executed in the model. In Section 4.4 we describe the design concepts we present the properties of the agents, and how all agents interact with each other and with the environment. In the following sections, 4.5 and 6.1, we elaborate on the the destruction of agents and the initialisation of the model. Finally, in Section 4.7 we divulge on the stochasticity present in the model.

4.1. Risk factors, entry points and hypothesis

In Chapter 3 we identified all relevant risk factors and entry points. During the data collection phase, we found there is not enough data available for some factors. We answered the first sub-question and second sub-question. Regarding the model, we can only include a subset of the identified risk factors and entry-points. The exact choices and the subsets are described in this section.

Before describing the choices, we present our hypothesis. Our hypothesis is based on the notion that frequent nudges regarding healthy behaviours are more likely to initiate long-term behavioural changes (Samdal et al., 2017). New, healthier behaviours need to maintained over time to become sustainable and repetition has been shown to accommodate this (Currie et al., 2013; Rothman et al., 2011).

How can recurring interventions targeting diet, exercise or smoking behaviours decrease the healthcare burden of cardiovascular diseases among women in The Hague?

Given the complex nature of the risk factors presented in Chapter 3, we have opted to only include clear risk factors for which there is a strong evidence base and for which we have enough data. We have opted to emphasise risk factors that contribute most to the risk of MACE. Obstructive sleep apnea, systemic inflammation, stress and stress/depression will will thus not be included.

Additionally, we excluded salt intake as BMI has been more prevalent in the literature results. We also excluded medication adherence for lipid metabolism, as blood pressure and glucose metabolism have been more dominant medical risk factors. We also decided to only include excessive alcohol consumption, and will not include the protective effect of light to moderate alcohol consumption.

Furthermore, we will not include all the identified relationships, but instead focus on the most significant ones, and, to simplify, change the paths of certain risk factors to the risk of first-ever MACE, such as pregnancy complications. Figure 4.1 shows what risk factors and relations will be included. The reason for this is that there is no consensus on some relations, and not all relations are deemed as valuable by the scientific community. Including these relations would make the model unnecessarily complex. Regarding the figure, the colours are only there to make the graph more legible.

Regarding the entry-points, we decided to include only energy expenditure, caloric intake, and smoking. The reason for this is threefold. First, there are enough data and theories about these three entry-points. Stress and alcohol consumption are two other interesting entry-point, but “stress” is currently still too abstract, and we lack data on both entry-points. Second, the identified three entry-points, are at the root of the problem. Figure 4.1 shows how these modifiable factors contribute to other risk

factors. Third, they make sense contextually. After all, health interventions in the Netherlands have been exploiting these entry-points for over multiple decades.

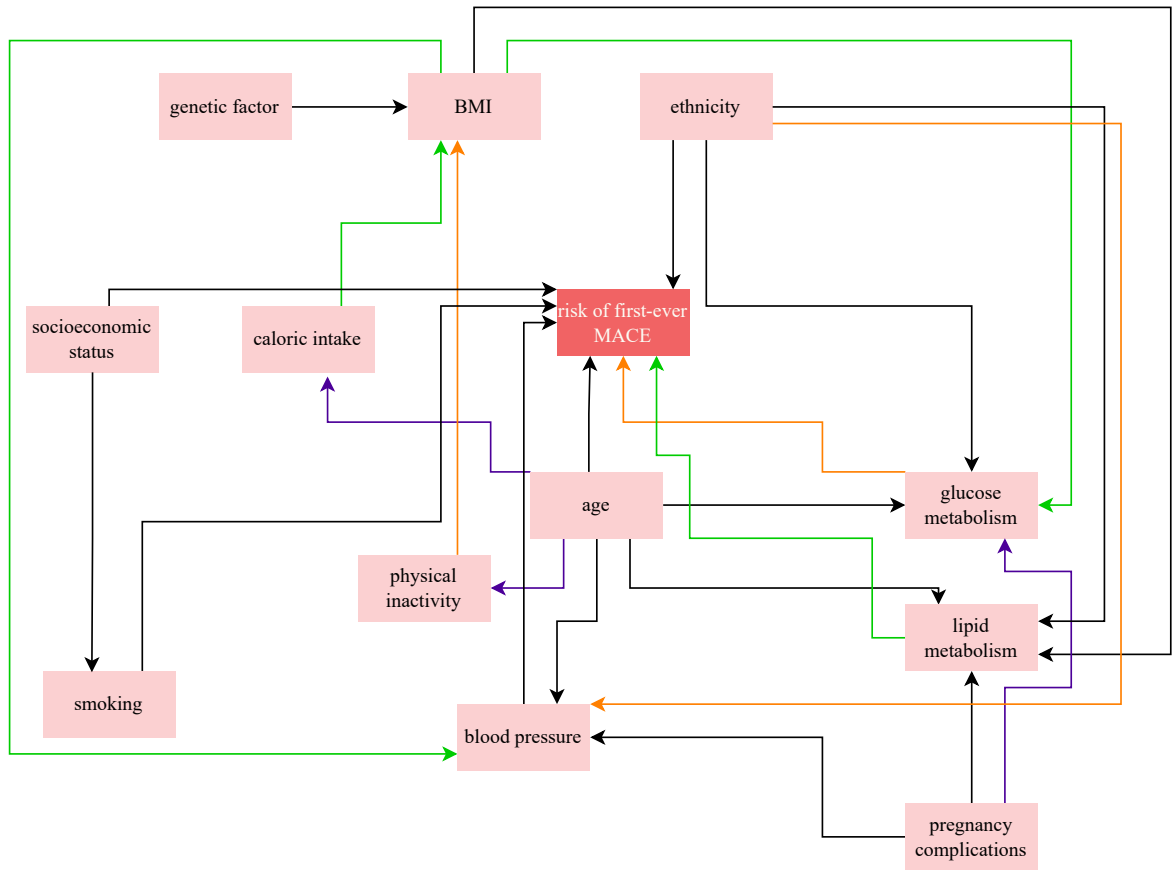

Figure 4.1: A directed acyclic graph showing the risk factors and the relationships included in the model.

4.2. Modeling approach

We aim to explore and interact with the spread of CVD-related health behaviours through the female population of the Hague. The analysis of the underlying mechanism of these dynamics and ways to influence these dynamics may help guide decision makers on what CVD policies to focus.

In Chapter 2 we established what health behaviours, social factors and policy outcomes need to be included to properly assess the course ahead for the Hague. We established the need to include the social relationships of women in Chapter 3, which adds a layer of complexity that cannot be properly implemented at the macro level of population dynamics.

The social circles of women have a non-uniform composition: they are comprised of people with different ethnicities, different BMIs, and different ages. Their social networks also have a dynamic nature as they change over time. These population dynamics can thus best be described at the individual level, where the actions of each women include a degree of stochasticity.

The stochasticity is also present in events such as becoming a mother, in the genetic factor that dictates how much impact a caloric deficit or surplus affects her weight, and to what degree she can be persuaded by her heterogeneous network to change her behaviours.

Because of the reasons listed above, we feel the agent-based modelling approach is a powerful and intuitive method to test hypotheses about policy outcomes, behaviours, and the dynamics that occur through interactions between women.

4.3. Process overview and scheduling

Changes in weight, BMI, blood glucose levels, cholesterol levels, blood pressure and cardiovascular risk are not immediate. They gradually change over time, hence why it was decided to choose a tick size of one month. This means that 12 ticks equal a year. Since the model runs from 2023 to 2070, the true runtime is 47 years. Since each step equals 1 month, that means the total runtime is $47 \times 12 = 564$ steps. Since it looks nicer, we have stated and will continue to state the model is ran for 50 years, even though it is truly 47 years.

The model keeps track of a schedule. On every tick, the schedule will execute one step of the model. The model is the environment in which the agents subside. The agents themselves represent the female population of the Hague. Within the step of the model, all agents on the schedule get to perform their own step. The order of the agents is random.

Every step the instantiation of the model class goes through a routine. Within that routine, all agents in the schedule are called upon to execute their own step. The step of each instantiation of the agent class is s displayed in the flow chart in Figure 4.3. Note that some decisions were taken to keep runtime down. An overview of the sequence of events is described in subsections 4.3.1 and 4.3.2.

4.3.1. Model's step

The events in Figure 4.2 show the order of operations of a single time step of the model class, the environment of the agents. Within this environment the agents subside. Every step, this routine will be executed. The asterisks in the Figure denote that the routine checks for the beginning of the year twice. Once **before** the steps of the agents have been processed and once **after**

First, when the model executes a step, if the year has just started, the model calls a subroutine that determines for the current and the subsequent eleven steps how many women should get pregnant. It randomly selects pregnant women out of a viable pool of agents.

If the instantiation of the model has been initialised with interventions, they will be processed in the next step. Specialised subroutines will be called depending on what interventions have been turned on.

Next, the model processes the influences the social networks of agents exercise on their lifestyle behaviours. For each agent the subroutine loops through her network to determine their new smoking, dietary and exercise intentions. The number of friends an agent has will vary based on her age, so the subsequent subroutines will remove random agents from a woman's network or connect women that are still looking for friends respectively. The latter subroutine also checks if potential friends meet each other's conditions. After this subroutine, all agents can perform their own step. This step is described in subsection 4.3.2.

After the agents have performed their step routine, the step of the model looks at whether it is the start of each year (again). Then, it calculates based on the number of scheduled agents how many instances of the agent class should be created to ensure the population growth matches the projections. This is done once per year to keep runtime down.

Finally, the model removes agents from the schedule that have died or suffered a MACE during the execution of their own step.

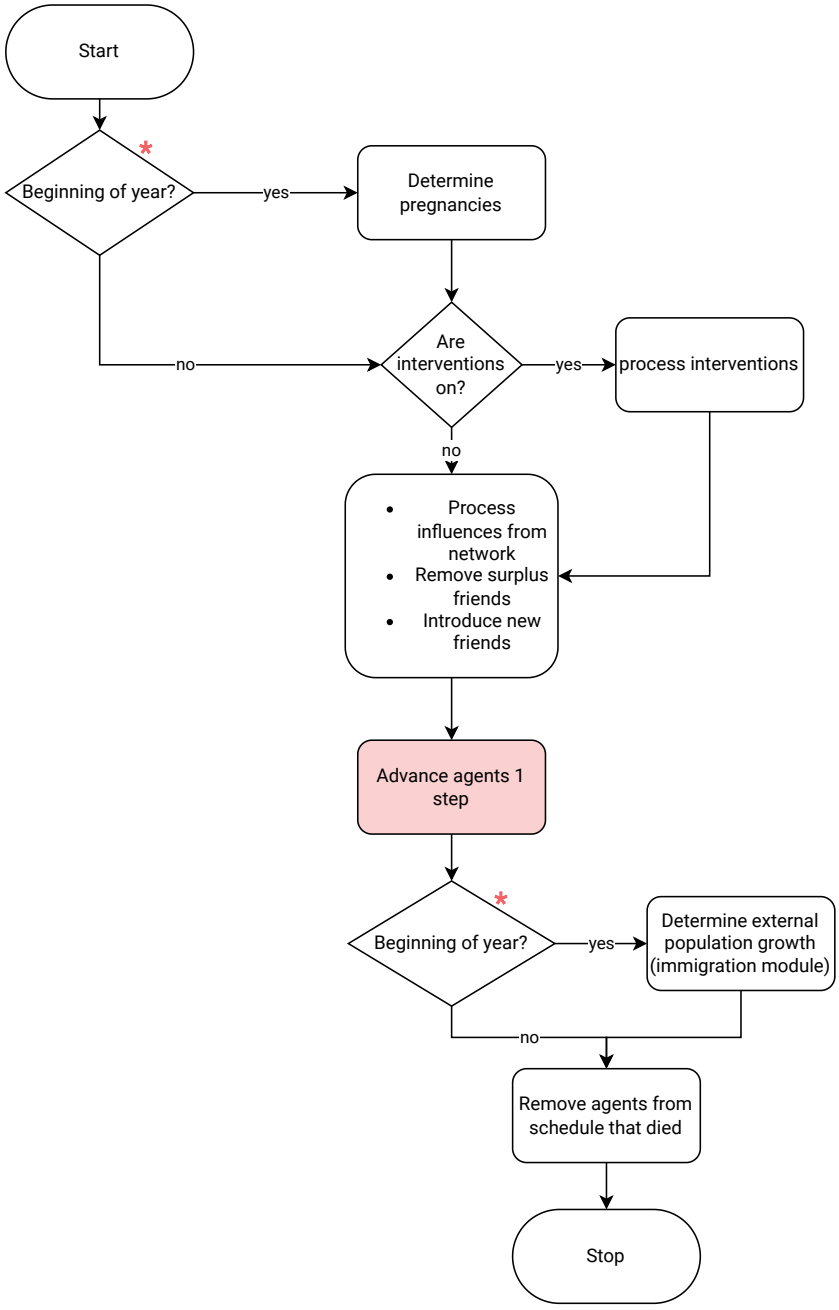

Figure 4.2: Rough outline of each step of the model.

4.3.2. Agent's step

The procedure described here is also shown in Figure 4.3. One can imagine this description and/or figure can be inserted in the pink rectangle of Figure 4.2.

A step for an agent describes multiple possible pathways. First it checks whether the agent should really be capable of doing a step. For instance, a dead agent should not be able to change her attributes. Then, if the month of the schedule matches the month of birth of the agent, the agent will age up. If an agent turns 110 years old, she is put on the list of deceased agents. If, however, an agent turns 12 years old, that means she is no longer influenced by her parents, but by her network, meaning the agent starts to get a social network of her own.

Following this, the agent gets to decide whether she wants to start smoking or stop smoking based on the influences from her network. After this, the model will check if an agent of 75 years or older will die in this year if the year has just started. This choice was made to improve runtime. If the model

determines the agent will die this year, it assigns a random month to the agent on which she will die. The model will also determine whether an agent will suffer from unintended weight loss due to depression in their later years.

If it is the agent's month of death, she will be put on the list of deceased to be removed from the schedule. If not, the agent may grow based on her age. Whether she grows or not, after this an agent may decide, on her own, to lose weight. Interventions will be processed if the model instantiation in which the agent resides has been initialised with interventions. Then, the model will calculate how the agent's health behaviours reflect on her weight, blood pressure, cholesterol values and blood sugar values. Then it calculates the 10 year risk of MACE incidence. Each agent keeps track of her MACE incidences. The mace incidence of step x will be used to calculate her risk at step $x + (12 \times 10)$.

Based on the mace incidences calculated in previous steps, the model will determine if an agent will get a MACE this step. This custom data structure defaults to use the 5 year incidence MACE risk that is calculated on the first step the agent is active if no MACE risk can be found. A random number is extracted from a uniform distribution between 0 and 1. If this number is below the MACE risk, the agent will be added to the list of agents that should be removed from the schedule, and will be added to the agents that suffered a MACE.

Finally, a pregnant agent will give birth if the current month is her due month. The class does not allow pregnant women to die or to get a MACE before giving birth.

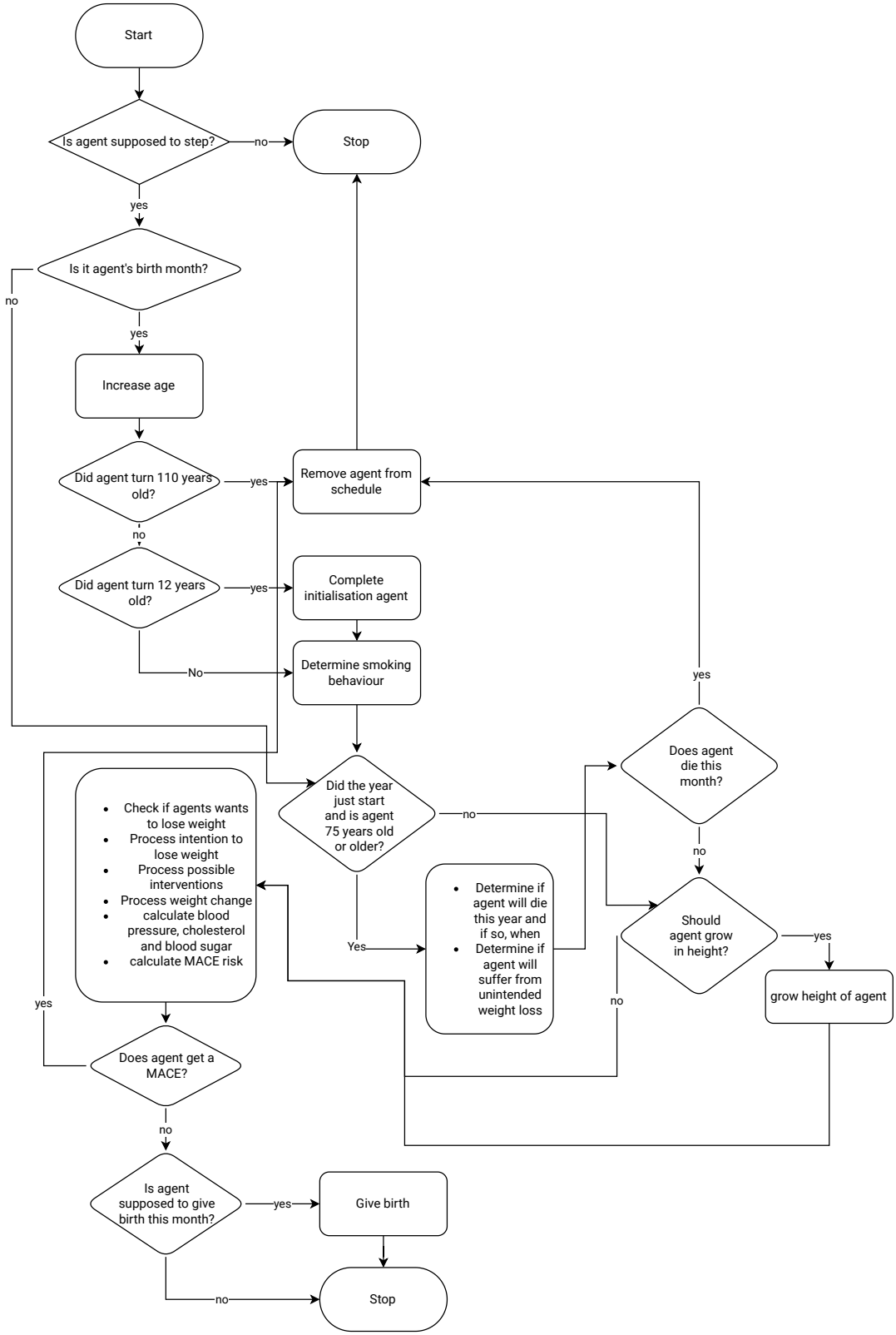

Figure 4.3: Rough outline of each step of an agent.

4.4. Design concepts

All agents that reside in the model environment have multiple attributes. Together, all agents represent the female population of the Hague. The attributes of the agents, and the way they are influenced over

time are described in this section.

4.4.1. Weight

In order to calculate the caloric expenditure of each female every month, the Equation 4.1 from Cutler et al. (2003) was used. We adapted it slightly to incorporate exercise as a multiplier of basal metabolic rate, since it is more intuitive and there are more data available on it. The notation used is summarised in 4.1. We opted to use the mean daily caloric value of each woman. Because of this, it is relatively easy to use the model to explore trends such as the recent higher consumption of sugar-sweetened beverages could and the overconsumption associated with the increase in eating out of home (Lachat et al., 2012).

$$K_{out} = E \times ((\alpha + \beta \times W) + SEE) + 0.1 \times K_{in} \tag{4.1}$$

where

Table 4.1: Notation for Equation 4.1

Symbol	Explanation	Unit
K_{out}	caloric expenditure	kcal/day
W	weight	kg
K_{in}	energy intake	kcal/day
E	energy expenditure multiplier	dimensionless
α	constant	dimensionless
β	constant	kcal/(day × kg)
SEE	constant	dimensionless

The equation encapsulates three ways to burn calories, namely: basal metabolism, digestion process and physical activity. Basal metabolism is the minimum amount of calories required to keep the body alive at rest and is given by the Schofield Equation: $BMR = \alpha + \beta \times W$. Digestion, which is the human body processing food is on average 10% of the caloric intake. The third way, physical activity, depends on the intensity and duration of the activity in question.

α and β were derived from literature (Schofield et al., 1985). The values for females are shown in Table 4.2.

Table 4.2: Values for α and β

Age	α	β	SEE
<3	-31.1	58.317	59
3-10	485.9	20.315	70
10-17	692.6	13.384	111
18-29	486.6	14.818	119
30-60	845.6	8.126	111
> 60	658.5	9.082	108

The standard error of estimation (SEE) allows us to account for different types of muscle builds. For example, if a person has a lot of lean muscle opposed to the average person of the same weight and height, then we will add the SEE to correct for this.

To calculate the weight of the agent, an equation from Ramirez-Nafarrate and Gutierrez-Garcia (2013) is used. We adapted it to include genetic variations, after all energy homeostasis is influenced not only by energy intake and expenditure, but also by one's metabolism and the proclivity to store excess calories in the body an (Chung & Leibel, 2008; Leibel, 1995). Quantifying this aspect has not yet been done before, as multiple genes are related to nutrient partitioning and metabolism (Magkos et al., 2016). Stunkard et al. (1990) show that only 66% of the BMI is determined genetics, or, better put, heritability. This is also shown in Equation 4.2.

$$W(t) = W(t-1) + (H(t) - H(t-1))\gamma + \frac{K_{in} - K_{out}}{\epsilon} \tag{4.2}$$

where

Symbol	Explanation	Unit
$W(t)$	current weight	kg
$W(t-1)$	weight last month	kg
$H(t)$	current height	cm
$H(t-1)$	height last month	cm
γ	average weight gain when growing one cm in height	kg/cm
K_{in}	food intake	kcal/day
K_{out}	caloric expenditure	kcal/day
ϵ	caloric gain equal to km gain	kg/calorie

The value for ϵ is based on Cutler et al. (2003) and Wishnofsky (1958 Sep-Oct), who state that for a typical person, an increase in calorie consumption of 7716 calories increases one's weight by one kg. To include the genetic variability, we assumed a normal distribution with a mean of 7716 and a variance of 500. γ was calculated using the 50th percentile in the growth charts from TNO (2010) and is shown in Table 4.3.

Table 4.3: Values for γ. For other ethnicities, we assume 0.516.

Nationality	weight	height	γ
Dutch	$70-5.5$	$185-60$	0.516
Turkish	$70-5.5$	$185-60$	0.516
Moroccan	$70-5.5$	$185-60$	0.516
Hindustan	$65-5.5$	$180-60$	0.469

Since we do not care about people becoming underweight, and we assume their effect on the population are minimal at best, women cannot become underweight in the model.

It is also well known that women, especially young adults, will have a tendency to try out diets, unprompted by their social circle (French et al., 1995). To implement this behaviour, we used the probabilities given in Blokstra et al. (1999). Unfortunately, the numbers do not take into account the reason of dieting: whether it is brought about by the social circle or an external factor. Every birth month, before the age of 45, every agent is assigned new dieting behaviours. In one extreme, an agent will not diet this year, on the other extreme, the agent will diet up to 10 months. The actual months in which dieting takes place are randI can omly determined. Within these months the agent will eat up to 500 calories per day less.

4.4.2. Height

The formula from Hermanussen and Cole (2003) is used to calculate the target height of a child based on the length of her mother and father (van Dommelen et al., 2012). It is shown in Equation 4.3

$$TH = 47.1 + 0.334 \times H_Y + 0.364 \times H_X \tag{4.3}$$

where H_X is the length of the mother and H_Y the length of the father. H_Y is drawn from a normal distribution.

The TH is used to calculate the target height range, THR. This area is defined as 2 SD around the TH. The equation for SD is shown in Equation 4.4. Accordingly, the model picks a value between $TH - THSDS$ and $TH + THSDS$.

$$THSDS = |\frac{TH - mean\_length}{SD}| \tag{4.4}$$

The growth at which agents grow is derived from the growth charts of TNO (2010). It is conditional on the age of the agent, and the equations for the quadratic regressions are shown in Table 4.7. We assume all women stop growing at age 21. The results of the data analyses to produce these equations are shown in Appendix C.1. We assume the formula, meant target height and SD for the Dutch are the same as for the other ethnicity.

Table 4.4: Equation showing the growth of women, mean target height and the standard deviation

Nationality	Equation	Mean target height	SD
Dutch	$-0.001855 \times t^2 + 0.886 \times t + 65.57$	170.7	6.3
Turkish	$-0.001966 \times t^2 + 0.8738 \times t + 65.43$	161	6.4
Moroccan	$-0.001927 \times t^2 + 0.8737 \times t + 65.11$	162.8	6.5
Hindustan	$-0.002095 \times t^2 + 0.9032 \times t + 63.77$	169.6	5.9

4.4.3. BMI

The Body Mass Index is calculated using the well-known formula shown in Equation 4.5.

$$BMI(t) = \frac{W(t)}{H(t)^2} \tag{4.5}$$

4.4.4. 10-year risk of first ever MACE

To get the probability of women getting a MACE in ten years we fitted a Fine and Gray model on data from Extramuraal LUMC Academisch Netwerk (ELAN) and CBS (Leiden University Medical Center, n.d.). The ELAN database contains data from GPs in the region of Leiden and the Hague. The database contains all International Classification of Primary Care (ICPC) codes that a GP has mentioned in a patient dossier, meaning that these are not just diagnoses, but also suspected and wrongful diagnoses.

We opted for this method as the currently employed CVD risk assessment tools focusing on 10-year CVD risk calculations have been shown to underestimate CVD risk in young to middle aged populations (Hobbs et al., 2010; Lloyd-Jones, 2010) and this allows us to incorporate risk-factors that have not yet been incorporated in previous CVD risk assessment models. Note that we do not care about recurring MACE events (Sakakibara et al., 2017).

More information on the data models can be found in Appendix C.

4.4.5. Fasting blood glucose, cholesterol, and blood pressure

To calculate the values for fasting blood glucose, cholesterol and blood pressure, a total of three generalised linear models (GLM) were fitted on data from the ELAN database and from CBS. These models allow us to asses which women suffer from (pre)diababetes, hypertension and dyslipidemia. A more in-depth description of these models can be read in Appendix C.

Note that the model not take into account other medical conditions. Based on the available data and the literature review, we decided to only use these three medical risk factors, and as such also did not incorporate Diabetes Type 1.

4.4.6. Smoking

When an agent's desire reaches a randomly defined threshold, the agent will change her behaviour. An agent can adopt four behaviours associated to smoking: she is not smoking, she has started smoking and she has kicked the habit. When an agent has kicked the habit, she can no longer start smoking again.

For women over the age of 18, the threshold is a random value between 0.32 and 1.3, for women under the age of 18, this value is between 0.063 and 0.7. This means all women under the age of 18 have the potential to smoke, whereas about 30% of the women over the age of 18 will never start smoking. These values are picked from an uniform distribution, either at initialisation, or when an agent turns 18 years old. The ranges are assumptions.

Once an agent starts smoking, the average smoking behaviour of her social network need to fall under a new threshold. This value is picked from a triangular distribution, with 0.6 as the lowest possible outcome and 0.8 as the highest possible outcome. The mode was determined to be 0.6.

Once an agent over the age of 18 starts smoking, about 20% of her network will start smoking as well within the same time step.

An agent is also able to start smoking on her own, due to external influences. In the agent's birth month, all non-smoking agents have a small chance of picking up the new habit. This probability is dependent on multiple factors. The first factor is the income of an agent: the lower the income, the higher the likelihood for an agent to start smoking. The second factor only applies to agents below the

age of 18. External factors, such as movies and influence from the internet, may drive a woman under the age of 18 to start smoking. We assumed the pattern shown in equation 4.6, where x stands for all time steps the model will run in total. Note that we floor this function with 0. The probability to smoke for agents aged 18 and older and under 18 are presented in Equations 4.7 and 4.8 respectively. The smoking multipliers are based on an assumptions and are shown in Table 4.5.

$$\texttt{external smoking factor} = (\frac{1}{2} \times sin(\frac{1}{40} \times x - 1.57) + \texttt{random.normal}(scale = 0.2, size = len(x)) + 0.5) \times 1.5 \tag{4.6}$$

$$0.1 \times \texttt{income multiplier} \tag{4.7}$$

$$0.2 \times \texttt{income multiplier} \times \texttt{external smoking factor} \tag{4.8}$$

Table 4.5: The income multipliers.

Level	Cut-off point	Value
0	$\texttt{income} < 31700$	1.4
1	$62700 \leq \texttt{income} \leq 31700$	1.25
2	$\texttt{income} > 62700$	1

4.4.7. Age

All agents have an age and a birth month. Although agents of younger than 12 are added to the schedule so that they can age, they do not interact with each other or with agents 12 years old or older.

Alibhai (2005) pointed out that it is common for elderly people to experience unintentional weight loss due to several diseases and disorders. They note that this happens primarily in people 75 years or older. Estimates range between 16%-35% of the female elderly to lose 5% of usual body weight over 5-10 years (Deeg et al., 1990; de Groot et al., 1996; Newman et al., 2001; Sørbye et al., 2008).

To implement this, at the start of each new year we look at the people aged 75 or higher. All of these have a probability to suffer from unintended weight loss. This probability is determined by Equation 4.9, where age is the age of the agent, and $year$ is the actual current year. The weight loss itself starts at a random month within that year, and is determined to be a value between 1 and 4 kg per month, until the agent's BMI becomes 20. During this period, the agent is no longer susceptible to influences from her social network and external influences.

$$(5.74490920e-07 \times \texttt{age}^3 + 3.96785538e-05 \times \texttt{age}^2 + 6.81189843e-04 \times \texttt{age} - 3.19688799e-01) \times exp(-0.0013771318811465964 \times \texttt{year}) \tag{4.9}$$

4.4.8. Social economic status

Social economic status has been argued to be a good proxy for available means and intelligence. (Kist et al., 2021) show there exists an inverse relationship between social economic status and CVD deaths. All agents have a certain income level which affects their 10 year-risk of getting a first-ever mace and to what extent they are tempted to start smoking based on external factors. All agents are associated with income level 0, 1 or 3. The actual meaning of these values is shown in Table 4.6

Table 4.6: The possible income classes of agents

Level	Cut-off point
0	$\texttt{income} < 31700$
1	$62700 \leq \texttt{income} \leq 31700$
2	$\texttt{income} > 62700$

4.4.9. Effects of of pregnancy

A woman may suffer from pregnancy complications during her pregnancy. The chance to get gestational diabetes per pregnancy is 7.5%, whereas the chance to get gestational hypertension or (pre-)eclampsia is 5%. These values were retrieved from the literature studies.

If an agent suffered from gestational diabetes, after 5 years her fasting glucose value will be 7 or higher, whereas an agent that suffered from gestational hypertension or (pre-)ecalmpsia will have a systolic blood pressure of at least 140.

4.4.10. Medication usage

There are two ways to control medication usage among agents. Both methods only run on the birth month of the agent. The first method makes use of the GLMS. The GLMS differentiate between people on and people without medication. This means that people on medication will always have "worse" values. This essentially means that we need to look at both the GLMs with and without medication to figure out if medication is in order. To this end Equations 4.10, 4.11 and 4.12 are used to get medication usage for fasting blood glucose, systolic blood pressure and total cholesterol respectively. The "value" functions refer to the GLMs, and the binary values refer to whether the GLM should check the value with medication (1) or without (0).

$$medication\_gluc(x) = \begin{cases} 1, & \text{if gluc\_value(0)} \geq 7 \text{ or gluc\_value(1)} \geq 7.78. \\ 0, & \text{otherwise.} \end{cases} \tag{4.10}$$

$$medication\_blood\_pressure(x) = \begin{cases} 1, & \text{if bp\_value(0)} \geq 130 \text{ or bp\_value(1)} \geq 140. \\ 0, & \text{otherwise.} \end{cases} \tag{4.11}$$

$$medication\_chol(x) = \begin{cases} 1, & \text{if chol\_value(0)} < 5.33. \\ 0, & \text{otherwise.} \end{cases} \tag{4.12}$$

The second method only looks at BMI to determine whether someone should start using medication. We use the values found by Brown et al. (2000), and we assume only 90% actually uses medication.

4.4.11. Population growth

Centraal Bureau voor de Statistiek (2019b) has predicted the population size of the Hague. Their projections were used to fit an exponential function to predict the growth rate of the population. The function and the data points are shown in Appendix C.2. We thus assume that the population grows according to the projections made by CBS and we assume that these projections are good to base further predictions on. The equation is shown in Equation 4.13.

$$Popgrowth(t) = -0.15917403 \times e^{-0.0053049 \times t} + 1.18092669 \tag{4.13}$$

It is also known that the composition of the population in the Hague will change (Gemeente Den Haag & DSO / Strategie, Externe betrekkingen, Portfoliomanagement en Onderzoek, 2021). To include this factor, we used data on the composition of the Hague in the past to predict the trajectory of the population (Den Haag in Cijfers et al., 2021). We also decided to assume the composition of the immigrating women will remain stable after 25 years. There was no specific data on the Surinamese population, so we opted to use data on the Hindustani population.

Table 4.7: Equations predicting the ethnicity of the immigrants.

Nationality	**Equation**
Dutch	$-0.0006304 \times t + 0.4388$
Turkish	$1.484e-05 \times t + 0.07605$
Moroccan	$3.059e-05 \times t + 0.05952$
Hindustan	$-3.535e-05 \times t + 0.03688$

The women in the model can get up to three children. To determine the amount of children we use Figure 2.7 provided in Gemeente Den Haag and DSO / Strategie, Externe betrekkingen, Portfoliomanagement en Onderzoek (2021) and the total fertility rate of 2019 in Centraal Bureau voor de Statistiek

(2022a). We divided the total fertility rate by 2, as we assume half of the people born are men. We can thus calculate how many children should be born each year with the equation shown in 4.14, where t is the number of years that have passed. Note that Figure 2.7 in Gemeente Den Haag and DSO / Strategie, Externe betrekkingen, Portfoliomanagement en Onderzoek (2021) stops in 2030, which is why we assume the birth rate stabilises after 10 years and will thus not change.

$$(45.2/2/1000) * e^{(0.019319122903085854 \times t)} \tag{4.14}$$

Hurd et al. (2009) show that many children indicate their parents are their role models. Girls tend to choose their mother as a role model (Galbo, 1986). So the eating and exercise behaviours of adolescent girls will be based on the behaviours of their mother. If their mother has passed away before the child reaches the age of 12, we assume that the last behaviours of their mother before she passed away were passed on to the child.

4.4.12. Social networks

The social network of an agent consists out of the set of agents with whom she has a direct personal relationship. Relationships that are not maintained and relationships on an acquaintance level are not considered relevant. In the real world, networks are in general local.

We define a tie between two women as a symmetric, irreflexive and anti-transitive relationship. This means that a woman cannot befriend herself, that friendships are always reciprocated, and that, although some small network properties do hold true, a woman may not be friends with the friends of her friend. All ties have a degree associated with them, which is equal for both friends.

As observed by Pinkster and Völker (2009), most social networks tend to be comprised from people with a similar ethnicity. Additionally, Moroccan, Turkish and Surinamese people in the Hague tend to have very few Dutch network members. They state that, including kinship ties, 84 % of a resident's social network is of similar ethnic background.

We also assume no networks are stable: the composition of a network will change according to age. To get the sizes of the social networks of the agents, we analysed the dataset supplied by K. Bhattacharya et al. (2016). The data show the number of friends without specifying their gender. To resolve this we multiplied the values by 0.675 (Laniado et al., 2016). This resulted in the table shown in Figure 4.4. The cuts were based on significance, i.e. we create a cut when we see a significant jump in the data. In theory, we could have calculated the mean and standard deviation for every year, and even for every month, but that would also increase runtime to the model. The calculated means and standard deviations means we are able to simulate the real-world evolution of social networks by reconfiguring the social networks accordingly. More information is provided in Appendix C.4. The data set confirms the notion that elderly have a smaller network size (van Tilburg, 1998).

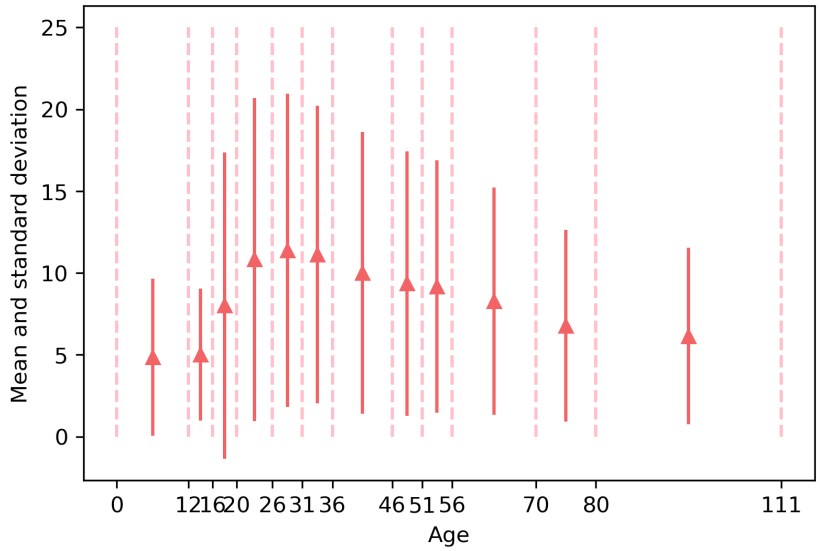

Figure 4.4: The mean and standard deviation of the number of friends per age group.

We also assume that people are born with an inherent need to always have relatively many, relatively few or a relative average number of friends. To achieve this we generate a random multiplier between $[-1, 1]$ when an agent is initialised. Then, this multiplier is used every time the agent reaches a new age cut and a new number of friends needs to be generated. This means that an agent will always have the same value between $[mean - sd, mean + sd]$.

Literature reports that individuals tend to prefer friends from the same ethnic background (Leszczensky & Pink, 2019). For this reason, we included the composition of the social circles of women. We analysed the data from the NEtherlands Longitudinal Lifecourse Study Survey (NELLS survey) (Tolsma et al., 2014). We want to emphasise that the survey was conducted over the Netherlands entirely. The dataset only includes data on Dutch, Moroccan and Turkish women, so we had to make assumptions for Hindustan women and women with another ethnicity. We found that the composition of the social networks are not really affected by age, as can be seen in Appendix C. We also found that most women tend to either befriend people from their own ethnicity, or people from the Dutch ethnicity. Hofstra et al. (2017) looked at the ethnic homogeneity of social networks of children on school, and they confirm this statement. They also found that networks from Hindustans consist of about 15% of other people with the same ethnic background, and the rest of their networks being primarily Dutch.

Next, we also included the finding from the literature study in Chapter 3 that people may tend to befriend people that have a BMI similar to them. We included this by introducing a bandwidth of acceptance, as shown in Figure 4.5. On the one end, women will only befriend women whose BMI differs only 10 points from theirs, whereas on the other extreme, women find a difference of 25 still acceptable. An agent will befriend a woman if her BMI falls below the agent's likelihood function and if the potential friend meets all other requirements.

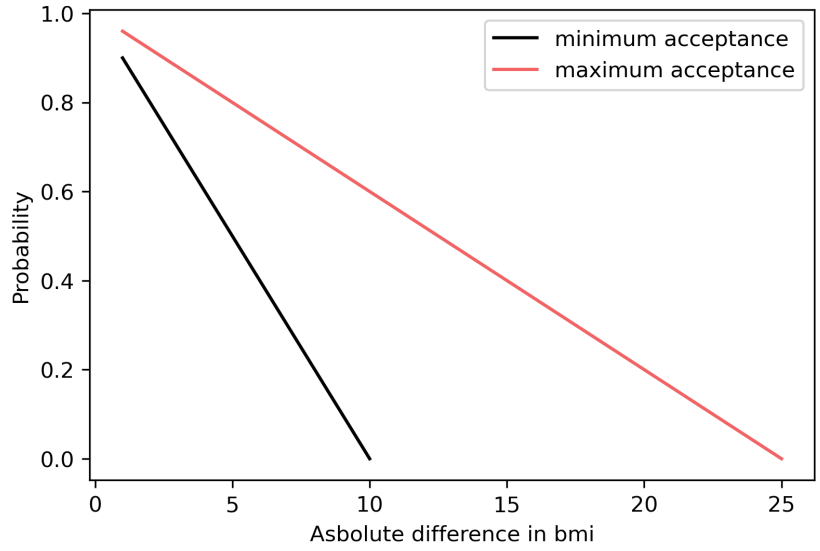

Figure 4.5: The two extremes of the likelihood to befriend function.

Furthermore, similar to BMI clusters, studies show that there are usually discernible clusters of smokers and nonsmokers in social networks (Christakis, 2008). Christakis (2008) hypothesise that the current spread of smoking cessation among adults can be explained by person-to-person interaction, and that because of this, whole clusters may stop smoking. We therefore hypothesise that new smokers are more likely to break ties with non-smoking friends and make ties with smoking friends.

4.4.13. Influence of network

Agents can influence each others food intake, physical activity levels and smoking behaviour. This has been incorporated similarly to Giabbanelli et al. (2012). Beheshti et al. (2017) claim it is one of the best models to simulate the spread of obesity-related behaviour. We have adapted their equations to include the weights as described in Christakis (2007). Equation 4.15 and Equation 4.16 show the influence of the network on agent i. The social network of agent i is denoted as F_i, with $|F_i|$ being the total number of contacts. w_{ij} is the weight of the relationship between agent i and j: the closer this

value is to 1, the more value agent i attaches to that relationship.

$$inf_E(t) = \frac{1}{|F_i|} \sum_{j \in F_i} w_{ij}(E_j(t-1) - E_i(t-1)) \tag{4.15}$$

$$inf_{K_{in}}(t) = \frac{1}{|F_i|} \sum_{j \in F_i} w_{ij}(K_{in_j}(t-1) - K_{in_i}(t-1)) \tag{4.16}$$

Finally, E and K_{in} are calculated according to Equation 4.17 and Equation 4.18 respectively.

$$E_i(t) = E_i(t-1) + inf_E(t-1) \tag{4.17}$$

$$K_{in_i}(t) = K_{in_i}(t-1) + inf_{K_{in_i}}(t-1) \tag{4.18}$$

We assume children between the ages 0 and 12 (excluding 12) are not affected by their social network, but by their guardians. Mei et al. (2018) show that a children's BMI from birth is primarily affected by the mother. Arredondo et al. (2020) also found a statistically significant correlation between overweight mothers and their children. Dereń et al. (2020) show that the majority of children will have a normal BMI, regardless of the BMI of the mother. The chance of a child being overweight or obese is however slightly increased if the BMI of the mother is elevated. To account for this, we use the distributions presented in their study.

For smoking, the desire to smoke of each agent is similarly determined by the influence functions of food intake and physical activity, as shown in equation 4.19. If the average of an non-smoking agent's friends desires goes above her randomly determined threshold, she will start smoking. Similarly, if the average desire of a smoking agent's friend falls below her threshold, she will quit smoking.

$$inf_S(t) = \frac{1}{|F_i|} \sum_{j \in F_i} w_{ij}(S_j(t-1) - S_i(t-1)) \tag{4.19}$$

4.5. Destruction of agents

Agents are removed from the model for one of two reasons: they get a MACE, or they die due to an unrelated reason. To calculate the average mortality rate we use data from Centraal Bureau voor de Statistiek (2022b). We extrapolated the data to include ages 99 to 110. We also calculate the growth rate from the life expectancy in the same dataset, and use this to reduce the mortality risk over time. We therefore assume people will be able to become older over time, as shown in Figure 4.6. The function was fitted to data, and shows the mortality risk of people aged 99 or older. The final equation is shown in Equation 4.20 with x being the age in months and t being the year.

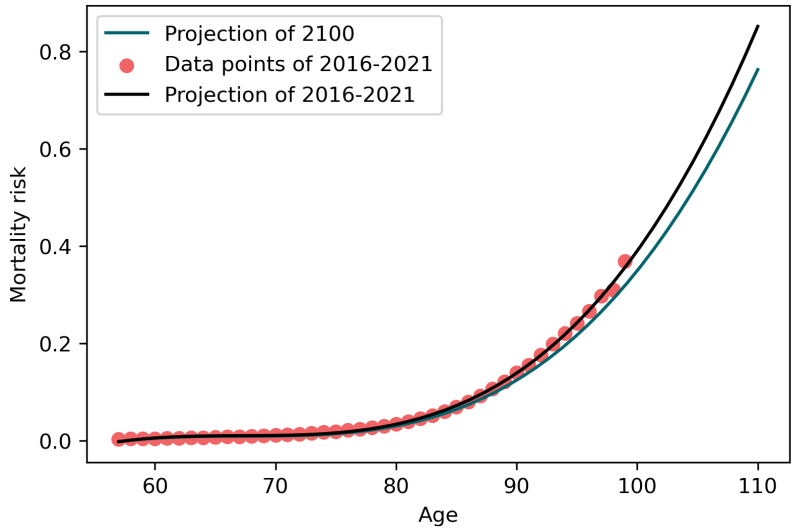

Figure 4.6: Predicted mortality rate of women in the Hague.

$$risk_i(x,t) = (1.06948768e{-}05{\times}x^3{-}2.15675241e{-}03{\times}x^2{+}1.45068422e{-}01{\times}x{-}3.24393183e{+}00){\times} e^{(}-0.0013765806311869483 \times t) \quad (4.20)$$

We also use the notion that people with obesity have a higher all-cause mortality risk of 1.10 (Janssen & Mark, 2007).

On every agent's birth month, the model calculates the agent's risk to get a first-ever MACE in 10 years. These will be used in 10 years to if she will suffer a MACE. In the 10 years there is no information on the agent's risk, the 5 year first-ever MACE risk will be used that was calculated on her first birth month. All MACE risks are multiplied by an "ethnicity multiplier", based on Kist et al. (2021)'s research. Once a year the model generates a random number between 0 and 1, and checks whether it falls below the risk. If it does, the agent suffers a MACE and is removed from the schedule.

4.6. Initialisation and input data

An agent can have one of the following nationalities: Dutch, Moroccan, Turkish, Hindustani or "other". The initial distribution of nationalities is determined by Den Haag in Cijfers et al. (2021). So, 43.8% of the population is Dutch, 7.6% is Turkish, 5.9% Is Moroccan, 3.6% is Hindustani and 39% is made up out of different ethnicities. For hindustanis we used (Oudhof et al., 2011), which shows that around 44% of Surinamese people in the Netherlands are Hindustani.

For the distribution over age groups we also use data from Den Haag in Cijfers et al. (2021). All ethnicity groups, initially, use the same distribution of age groups. We would like to emphasise that this may not be completely true to reality.

To get the initial overweight and obese portion of the population we use values provided by (GGD Haaglanden, 2020b). We did assume the data on 2 to 3 years-olds is also valid for 0 to 2 year-olds.

The model always tries to link a child with a mother, both at initialisation and when a child moves to the Hague. However, this may not always be possible if there are not enough adults. In such cases, the child receives a randomly generated BMI at age 12.

It is assumed agents try to keep their weight constant at initialisation, meaning that we can use Equation 4.1 to calculate the value of K_{in} to ensure the weight of an agent does not undergo any change. Effectively, this means we calculate the metabolic rate. The equation for this is shown in Equation 4.21.

$$K_{out} = E \times ((\alpha + \beta \times W) + SEE)/0.9 \quad (4.21)$$

To determine the activity level of women, we use the distributions provided in table 27 in the appendix of DESAN Research Solutions (2019). This means we did not include the notion that people with an

increased BMI, have a decreased tendency to exercise (Carneiro et al., 2016). We associated the frequencies with the multipliers provided by Harris and Benedict (1919). The initial multipliers are listed in Table 4.8.

Table 4.8: Estimated homogeneity and presence of Dutch people in social networks.

Activity level	**Frequency**	**Multiplier**
Sedentary	never	1.2
Lightly active	<1x per month	1.375
Moderately active	< 1x per week	1.55
Very active	1 or 2 x per week	1.725
Extra active	> x 2 per week	1.9

To include data on income, we analysed data available at CBS. We categorised the data set according to the cuts provided in Centraal Bureau voor de Statistiek (2019a) . So the groups are comprised out of people earning less than 31700, between 31700 and 62700 and more than 62700. The distributions can be found in Appendix C.

To get the current smoking behaviours of women in the Hague, numbers were used from GGD Haaglanden (2020a).

To cut down on runtime, during initialisation, it is determined how many friends that agent will have over her life.

4.7. Stochasticity

The underlying real-world system includes seemingly random elements, which result in stochastic parameters in the model. This essentially also ties in the sensitivity analysis described in Chapter 6 and Appendix B, as some uncertainty is the result of stochasticity of parameters. The analyses described in those chapters are therefore multi-purpose: they will account for the contribution of stochastic terms, and they will account for the contribution of assumptions.

The model considers stochasticity mostly regarding demographic and behaviourial elements. Additionally, things such as the rate of the actual weight loss as a result of unintended weight loss in women older then 65 years are also determined randomly. We have listed all the stochastic elements below:

- Dieting behaviour of women between the ages of 18 and 45.
- The numerical threshold for a women to commence and quit smoking.
- The standard error of estimation of Equation 4.1
- Although bounded by actual numbers, essentially, the number of friends is determined randomly.
- The women a woman will befriend is determined randomly.
- The tolerance of each agent of people with regards to women of vastly different BMIs
- The extent to which a woman can be influenced by external smoking factors.
- The susceptibility of a women to the influence of her network
- The unintended weight loss an agent aged 65 or older may experience. Both when this will occur is happen, and the actual weight loss: an agent will lose on average 1 to 4 kg per month.
- Which women will become pregnant and when they will give birth

For every run, a new seed will be set to initialise the pseudorandom number generators in the model. This means that the randomness will vary for all the elements described above in all runs.

5 Experimental set-up

To show the usefulness of the model, we subjected it to four different interventions. In this chapter we describe the experimental design, which includes the attributes that will be affected by the interventions, and the virtual scenarios that have been used during the experiments. The scenarios and interventions are inspired by both Figure 2.3 and the hypothesis. The scenarios are external factors, and we have opted to include a subset of all possible scenarios. The interventions make use of the intervention entry points identified for sub-question 2.

5.1. Settings

Experiments were ran with a time horizon of 50 years. All experiments were ran 100 times.

5.2. Scenarios

The model simulates three different smoking scenarios that are different with regards to smoking and susceptibility. The values of the scenarios are expressed in dimensionless numerical values, and are as of now, hard to equate to something concrete. This is a limitation of the model that is addressed in the Chapter 8.

The first and third scenario determine a woman's threshold to start smoking randomly between [0.063, 0.7]. Her threshold to stop smoking lies between [0.6, 0.8]. In the second scenario, the threshold to start and stop smoking is randomly placed within [0.063, 0.4] and [0.4, 0.6] respectively. The third scenario makes women more susceptible to influence from her social network. Her susceptibility is now randomly determined to be between [0, 1.2], opposed to [0, 1] for the other two scenarios. If her susceptibility is above 1, this means she is always susceptible to behavioural changes prompted by her social network's average. Additionally, this scenario allows women to change their caloric intake twice as much as the other two scenarios, namely a maximum of 1000 calories.

5.3. Interventions

This section describes the interventions that exploit the policy entry points as described in Chapter 2.

5.3.1. School education

Literature shows that education on weight loss can be an effective way to reduce weight loss short-term (Mazloomy-Mahmoodabad et al., 2017). The model allows us to explore the effects of these policies over a longer period of time.

School education focuses solely on dieting behaviour. All women with an age in the closed interval $[12, 16]$ years, who have a BMI over 25 will adjust their diet to lose 2 kg a month. In the experiments we opted to only control the frequency, duration, and the reach. All women that have been reached by the intervention will become less susceptible to influences from their social circle. The effects of the intervention will last after the intervention has been completed, unless it has been nullified by the influence of the social circle. The attributes that are manipulated during the experiments are shown in Table 5.1. We subjected the virtual population to the sets of values shown in Table 5.2.

Table 5.1: The attributes of the intervention that promotes education and guidance for young adolescents that can be influenced.

Name	Explanation	Unit
Frequency	The frequency of which the policy is repeated.	Array of months
Duration	The duration of the policy.	Months
Reach	The portion of women aged between 12 and 16 that will be affected (approximately)	Dimensionless

Table 5.2: The manipulatable attributes of the school intervention.

Name	Frequency	Duration	Reach
1	[1, 13, …, 589]	2	0.4
2	[1, 13, …, 589]	6	0.4
3	[1, 37, 73, …, 577]	5	0.9
4	[1, 7, 13, …, 595]	1	0.3

5.3.2. Smoking

To test the effectiveness of a policy solely focussing on the biggest risk factor as identified in the Fine and Gray model, we decided subject the virtual population to a policy that reduces the interest for women to pick up a cigarette and makes them more likely to quit. The policy is associated with the three attributes explained in Table 5.3. To be specific, we tested the configurations presented in Table 5.4.

Table 5.3: The manipulatable attributes of the intervention that solely affects smoking behaviours of women.

Name	Explanation	Unit
Frequency	The frequency of which the policy is repeated.	Array of months
Range of effectiveness	The policy introduces, essentially, a push factor to keep people from desiring a cigarette. The actual effectiveness of this push factor lies between two values that determine its range.	Dimensionless
Duration	The duration of the policy.	Months

Table 5.4: The manipulatable attributes of the smoking intervention.

Name	Frequency	Range of effectiveness	Duration
1	[1, 13, …, 589]	(-0.3, 0.1)	3
2	[1, 13, …, 589]	(-0.1, 0.1)	3
3	[1, 13, …, 589]	(-0.1, 0.1)	1
4	[1, 37, 73, …, 577]	(-0.1, 0.1)	6

5.3.3. Targeted approach

Given that in the real world resources are limited, it is interesting to explore an intervention that only targets the communities that need it most. This intervention is bound by the number of people for which there are resources available. In our specific implementation, the intervention selects the communities that are most at risk. These communities are identified from the social network every m years by clustering algorithm, after which n women will be selected. Then, the 10-year first ever mace risk is used to identify the communities that are worst off.

To find the communities that are worst off, we use the Louvain method (Blondel et al., 2008). Then we score all communities based on the health attributes of the nodes in the communities. Then the top communities that have a total of about n women will improve their lifestyle behaviours based on the average behaviour within the cluster. To be specific, they will reduce their caloric intake with either 300 to 500 calories, and they may increase their caloric expenditure if they lived a sedentary life.

We tested the intervention with a varied number of n, namely: 50, 100, 200, 300 and 500. For m we used either a frequency of one year or of four years. Four years was chosen, as that is the general duration of a municipal council, meaning that every four years, there should be opportunity to perform

a big reappraisal of the health status of the public. The variations of the interventions that will be tested are shown in Table 5.5.

Table 5.5: The different variations of the targeted approach.

Name	number of people (n)	Frequency (m)
1	50	4
2	200	4
3	200	1
4	400	4
5	400	1

5.3.4. Immediate approach

The immediate approach is an intervention that immediately, on the first time step, reduces the percentage of adult women that are either overweight or obese to 30%.

6 Implementation, validation and verification

In this chapter we present details on the implementation, validation an verification of the model that was used to explore the hypothesis: *How can recurring interventions targeting diet, exercise or smoking behaviours decrease the healthcare burden of cardiovascular diseases among women in The Hague?*.

6.1. Implementation

The implementation of the formalisation described in Chapter 4 was done in Python 3.10.4. The classes for agents and their environment, the model, were built under object-oriented paradigms. Agents interact with each other and with the model class. The input values are described in Section . We made grateful use of the MESA package (ver 0.9.0) and its RandomActivation schedule.

The model and all associated files for the experiments, visualisations, and data analyses, unit tests, sensitivity analyses have been placed on a repository on Github, and can be accessed at:

https://github.com/Lischip/pulse_ultra

6.2. Validation and verification

Validation aims to establish that the model that was implemented is sufficiently accurate for the purpose for which it was intended (Senge & Forrester, 1980). We defined the purpose of the model in the conceptual phase described in 2. Validation of the model proved to be a challenge for three reasons. First, it was a challenge to obtain enough qualitative and quantitative information on women's behaviours and data in general, meaning that some important aspects were omitted. Second, as a partial consequence, when we presented the emergent behaviour to experts in the field, they agreed with the behaviour, but could not tell whether the interactions and assumptions are actually the **right** ones that actually cause the emergent behaviour we see in the real world. Third, agent-based modelling is a rather novel concept for the health specialist and social network specialists that were approached for feedback. This introduced an additional hurdle to understanding the methodology. Once that hurdle was passed, the next hurdle was explaining the rather intricate model.

Verification aims to ensure that the formalisation that is described in Chapter 4, was accurately translated in a computer model (Ngo & See, 2012). In our case, validation and verification were performed hand in hand. If the model or a module resulted in unexpected behaviour, that could either imply our implementation was incorrect (unverified) or that our conceptual model needed adjustment (invalid). This resulted in an iterative process of continuously tweaking the model described in Chapter 4.

We performed white-box verification and validation was performed by checking the effects of each separate module. We also made sure to properly document the assumptions in case there were multiple ways a module could meet its specification, in which case a choice had to be made. The unit tests developed for this purpose were also used to check whether the implementation was correct. Unit tests were developed to check if birthdays had the desired effects, to verify the social networks, to check if the smoking behaviours made sense, to check if BMI, weight and other risk factors made sense, and to check if custom data types function correctly. All these unit tests were passed.

Black-box validation and verification was performed by collecting feedback from experts in the field, and by comparing some of the values against projections and statistics from other sources, such as the works from Rijksinstituut voor Volksgezondheid en Milieu (n.d.) and de Boer et al. (2019). The experts helped expose mechanisms from the real world that the literature study did not reveal, such as unintended weight loss, and the comparisons of the prevalence risk factors emerging from the model with past data and future projections made by the sources cited above were either explainable or did not deviate too much. It was however clear that the projections were not that reliable. For example, they would assume smoking behaviour among children would remain constant. However, we spoke with experts and read articles that suggest vaping could be a gateway tool to introduce children to smoking, thus increasing the total number of smokers among the youth, which would also increase the total number of female adult smokers (Chatterjee et al., 2018; Prieger, 2020).

For verification purposes, we also visualised the social networks. One such an example can be seen in Figure 6.1. The light green, blue, orange, dark green and pink colours represent women from Dutch, Turkish, Moroccan, Hindustan and other ethnicity. The size of each node represents the relative BMI. All the nodes on the outside are mostly elderly who have lost their social networks, women with a very small amount of friends, and women who were unable to find friends that meet their requirements. We can see clear clusters based on ethnicity. Similarly, we can see the effect of age in Figure 6.2. The more intense the colour orange, the older the node.

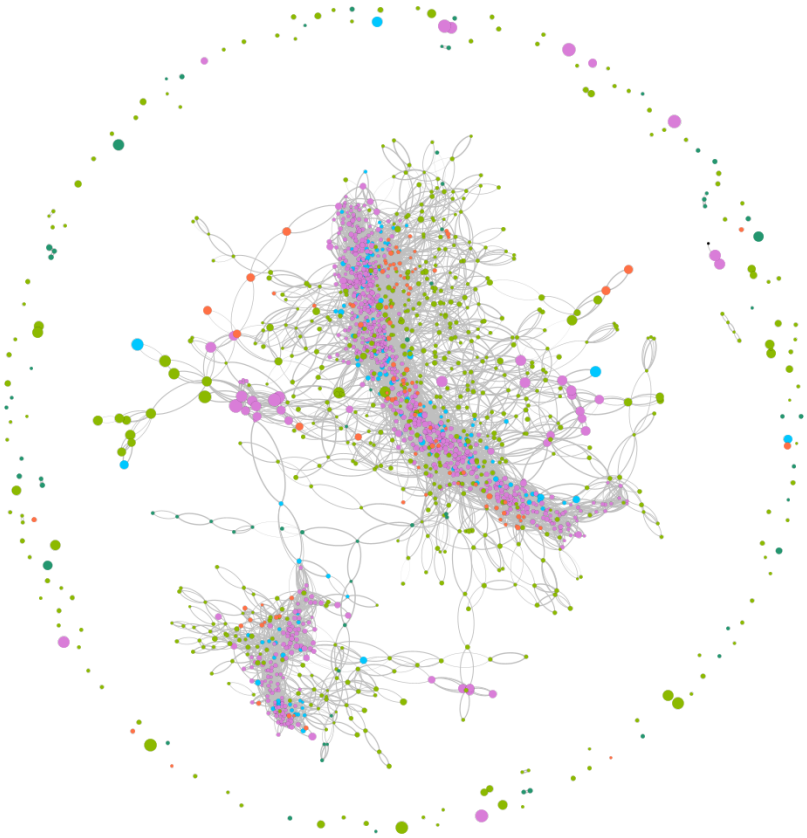

Figure 6.1: The ethnicities of the social network at initialisation.

Figure 6.2: The ages of the women in the social network at initialisation.

6.3. Sensitivity analysis

The goal of a sensitivity analyses is to show how sensitive a model is to parametric or structural changes (Cariboni et al., 2007). The goal of an uncertainty analysis is to show how the model reacts when structural and parametric assumptions are changed (Saltelli et al., 2019). In our case, there is overlap, hence why we combined the two in one big analysis.

Thissen and Walker (2013) describe that there are five levels of uncertainty. Level 1 uncertainty is the situation where we are not a hundred percent certain, but we are unable to measure the uncertainty in an explicit way. Level 2 uncertainty means we know there are alternate futures, and what the likelihood of these alternatives are. Level 3 uncertainty means we also know alternative futures, but we can only rank them. Level 4 means we cannot even rank the possible alternatives any more, and level 5 means we cannot even enumerate all alternatives. We have listed the uncertainties in Table 6.1. Note that immigration and intention are structural uncertainties opposed to parametric uncertainties. These are modules of the model that we can turn on or off.

Table 6.1: The uncertainties classified according to Thissen and Walker (2013) and our solutions

Uncertainty	Type	Solution
Age difference	4	Sensitivity analysis
Immigration	5	Sensitivity analysis and transparency (assumptions)
Intention	5	Sensitivity analysis and transparency
number of agents	0	Sensitivity analysis
Susceptibility	4	Sensitivity analysis and transparency
Tolerance of difference BMI	4	Sensitivity analysis and transparency
Future death rate (unrelated to CVD)	5	assumptions

6.3.1. Global sensitivity analyses

We employed a global approach to estimate the effects of the uncertainties on eight KPIs. We computed the Extra Trees feature scoring algorithm of the EMA workbench (Kwakkel, 2017). We employed this algorithm in two ways. First, we look at the extend certain KPI are affected by varying the parametric space of the parametric uncertainties and by turning structural uncertainties on or off. Second, we look at the effect of the uncertainties on the average MACE risk over time.

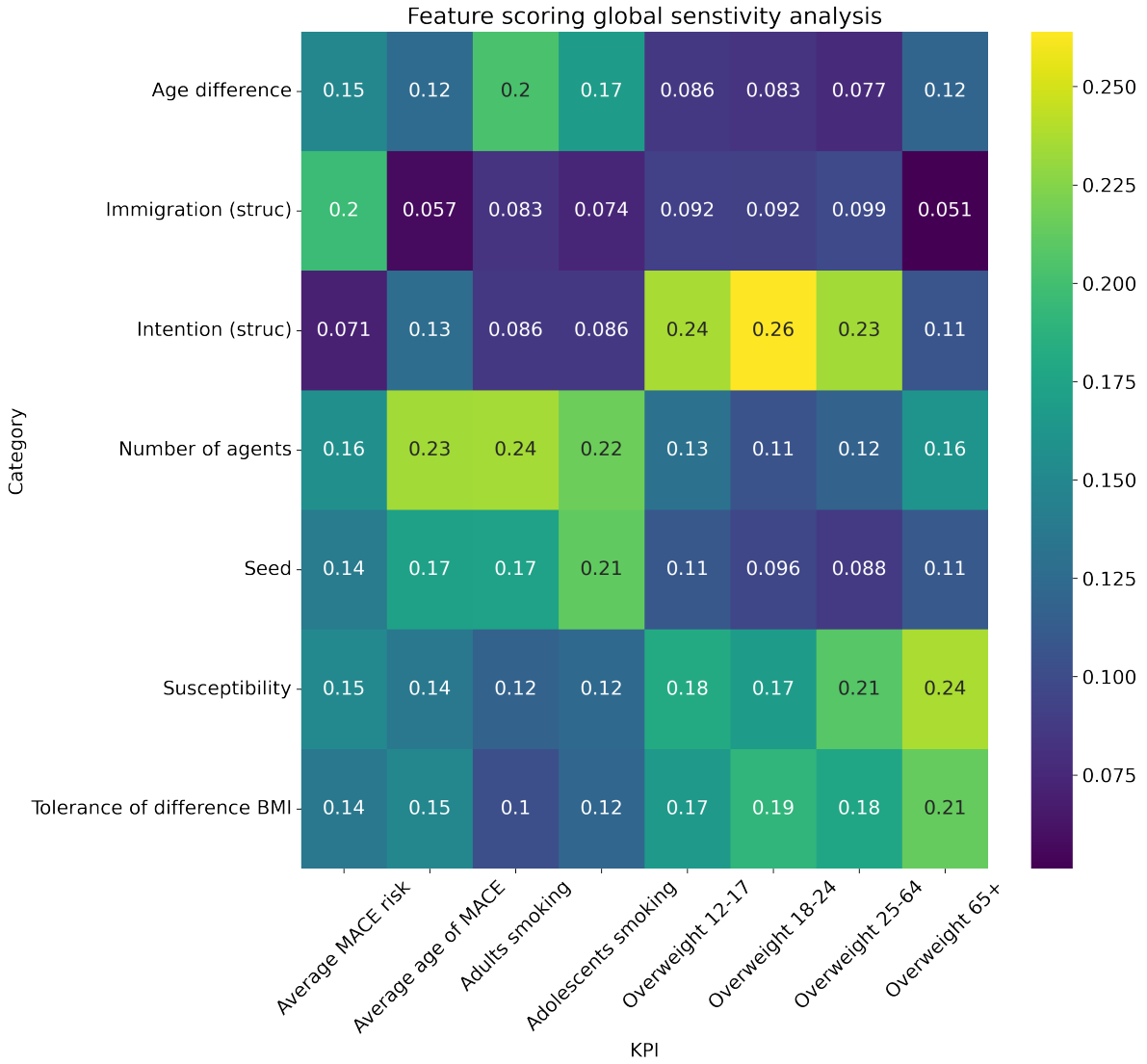

Figure 6.3: The effect of numerical and structural changes to the KPI.

In Figure 6.3 we show the effects of changes in the parametric space of the parametric uncertainties and by turning the structural uncertainties on or off. The Y-axis shows the uncertainties, whereas the X-axis shows the KPIs. We used the final values at the end of the run for all KPIs. The average MACE risk, which is the average MACE risk of all women, is very sensitive to the Immigration module being either on or off. The Immigration module adds agents to the model to fill the difference between the population size and the projected population size. The other KPI are not that sensitive to this uncertainty being turned on or off.

The overweight KPI (which also includes women who are obese) is primarily sensitive to susceptibility of women to influences from her network, the tolerance of women with different BMIs, and the intention to lose weight. The Average MACE Risk, the average age of MACE, adults smoking and adolescents smoking are mostly susceptible to the number of agents.

We also explored the seed. The seed is not an uncertainty, but the value that determines the values

of all samples that are drawn in the simulation. In Section 4.7, we discuss the stochasticity present in the model. Every run, the model will have a different seed, leading to different results each time. Women being overweight are not that much affected by a changing seed, whereas the other four KPI are.

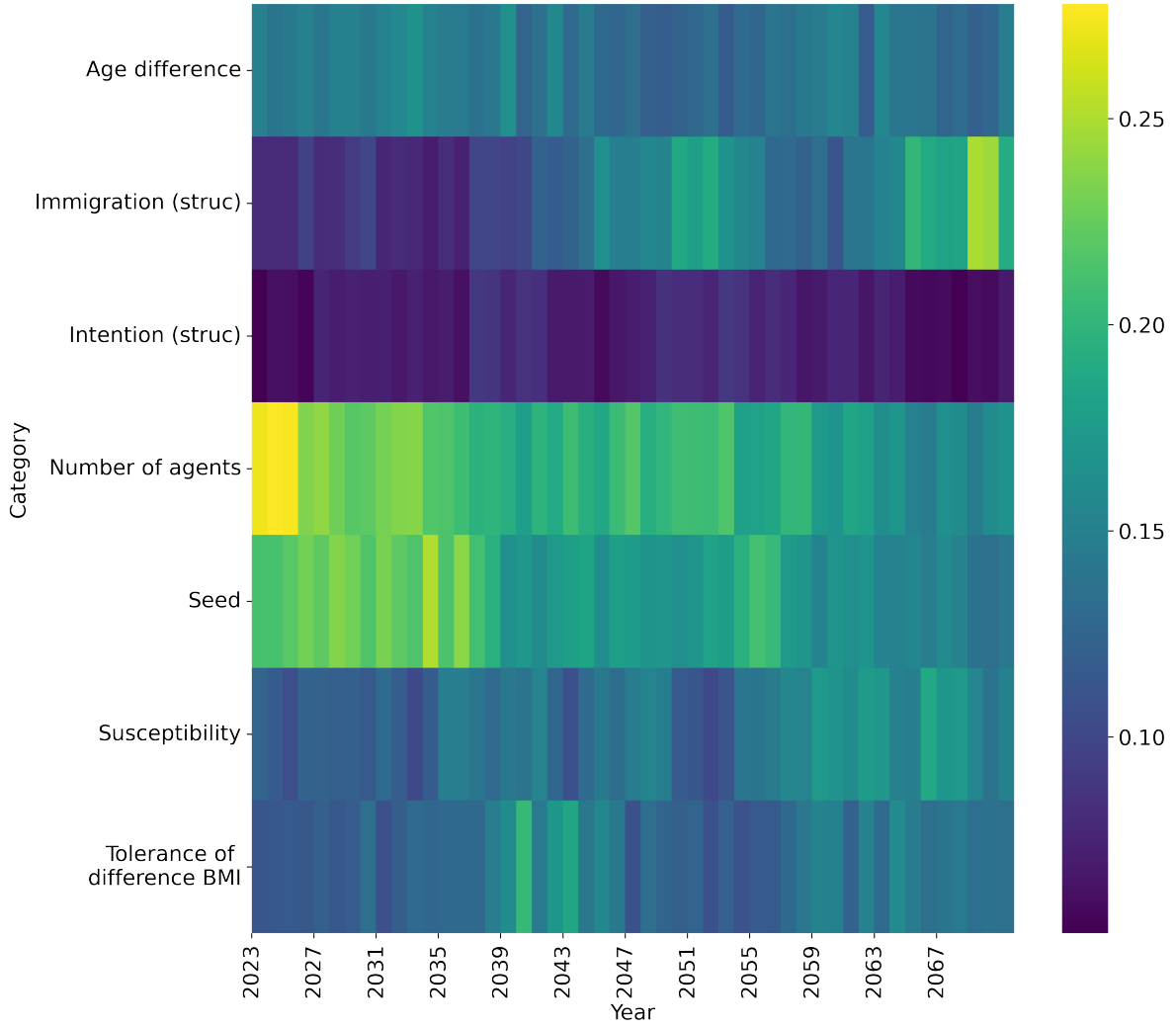

Figure 6.4: The effect of numerical and structural changes to the average MACE risk over time.

As explained in Chapter 4, there are some factors that essentially guide population growth. The model assumes there is an influx of people, both from births and from immigrations. The input values also indicate that the population will be ageing, which will affect the social networks. The number of friends is determined by the age of the woman. This is why we are interested in the sensitivity of the model over time. The results of this are shown in Figure 6.4.

The figure shows that for most uncertainties, the KPI is more sensitive at the start of the run then at the end. The two exceptions are the Immigration module and the Susceptibility module.

6.3.2. Local sensitivity analysis

The results of the local sensitivity analysis are described in depth in Appendix B. Here we provide a brief summary.

The local sensitivity analyses were performed on the same variables as the global sensitivity analyses except for the seed. The figures presented in Appendix B show that the variables are all more sensitive for variations at the start of the run than at the end. Over time, the band of possible outcomes seems to converge.

6.3.3. Fine and Gray sensitivity analysis

We performed a sensitivity analysis on the Fine and Gray Model as described in Appendix C.6. The results are shown in Figure 6.5. We present a heatmap: the Y-axis shows the input variables, the X-axis the independent variable. We see that age has the strongest correlation to the target variable: the 10-year risk of a first-ever MACE. The second highest risk factor is the smoking variable, which is modifiable.

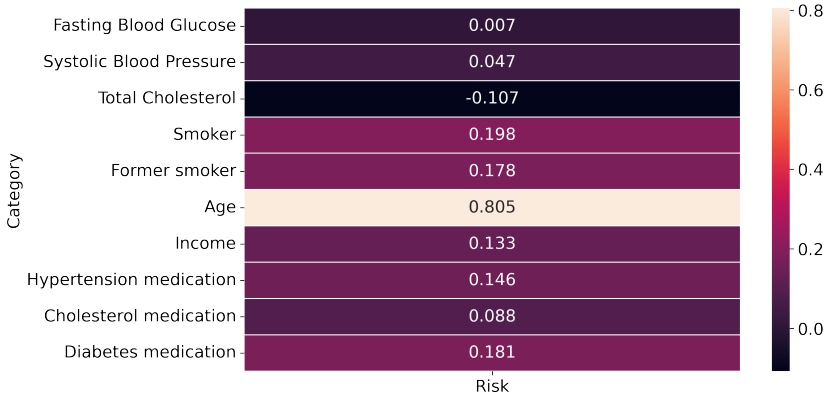

Figure 6.5: Sensitivity analysis results of the Fine and Gray model

BMI is determined by caloric intake and energy expenditure and affects three out of ten dependent variables. Therefore, this factor is actually quite potent to determine the 10-year first-ever MACE risk. Total cholesterol is negative in Figure 6.5, as a higher total cholesterol results in a decreased risk, whereas the opposite relation is true for the other variables.

7 Simulation and data model results

In this chapter we explore two sub-questions. The first being, sub-question 3. What is the expected future of cardiovascular diseases in women in the Hague in 50 years?, for which we subject the model to several scenarios, and disect the results. For sub-question 4. From both a policy and a healthcare perspective, what is the way forward regarding cardiovascular diseases among women? we investigate the effects of several interventions exploiting the entry-points detected in Chapter 3.

7.1. 10-year risk of first-ever MACE

In Chapter 4 and Appendix C.6 we describe the Fine and Gray model that was developed to calculate the MACE risk for all agents in the model. In Figure 7.1 we show the risk of two women over their life (from age 15 to 100). The first woman has a systolic blood pressure of 110, a fasting blood glucose of 5.66, a total cholesterol value of 5.44, and does not smoke and has not smoked in the past. The second woman has a systolic blood pressure of 160, a fasting blood glucose value of 9, a total cholesterol value of 5.44, and has smoked and is smoking. Both are in the highest income class. The X-axis presents the age and the Y-axis presents the risk. The figure clearly shows that multiple risk factors are relatively more dangerous for younger women than for older women, where age seems to be more dominant than the combination of modifiable risk factors.

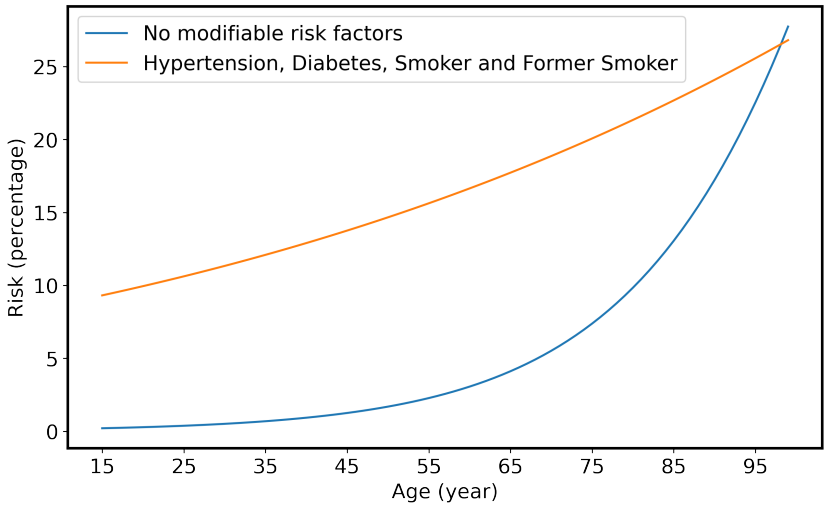

Figure 7.1: The 10-year risk of first-ever MACE for two different women over their life.

7.2. Base case

To explore the effects of the different scenarios on the base case we look at several KPI. Figure 7.2 shows the average number of MACEs per scenario per age group per period. Every graph shows a different time period. In each graph, the x-axis is comprised of the age groups and the y-axis shows the KPI, the actual percentage women per age group that suffered a MACE in that period.

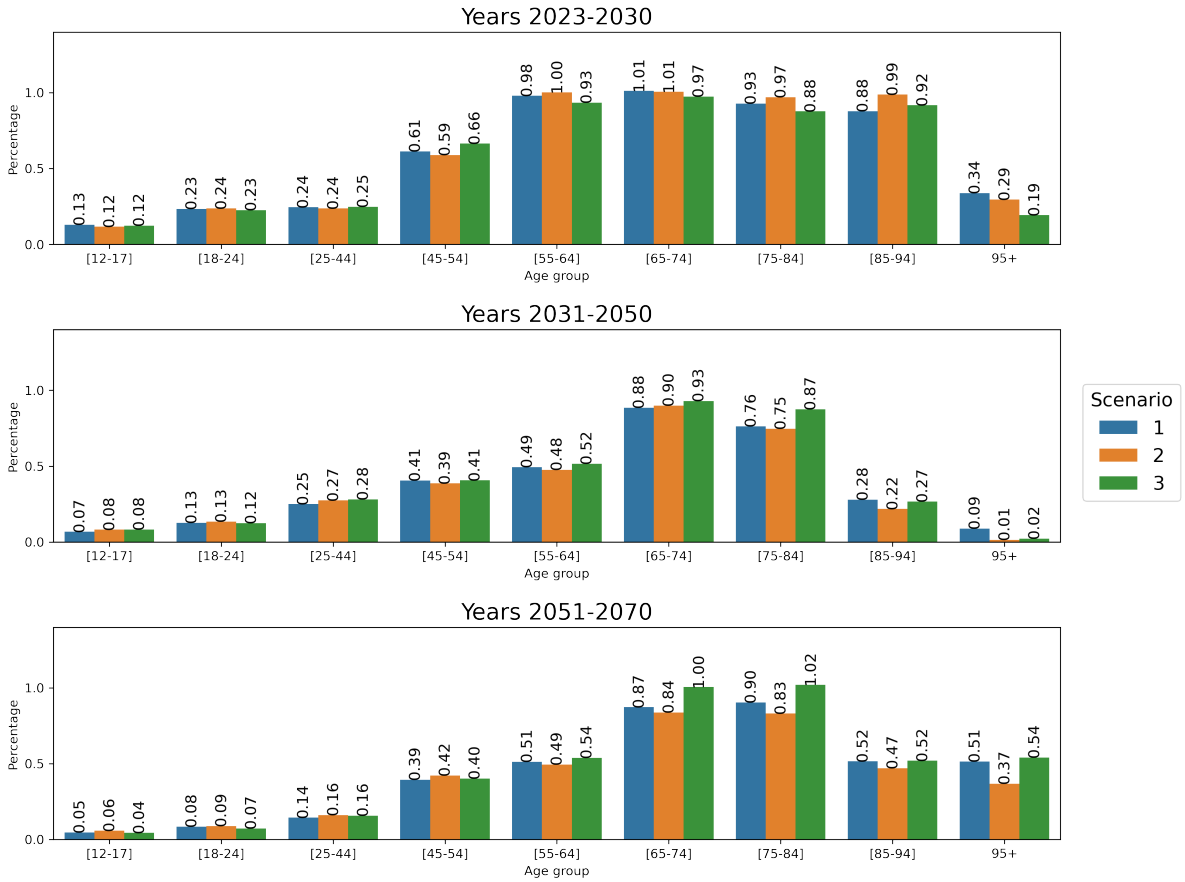

Figure 7.2: The average percentage of women getting a MACE per year per period.

The first graph shows the first seven years. The second scenario results in the most average MACEs per year, but only marginally. In all scenarios, most MACEs relative to the size of the age group occur in the age groups [55-64], [65-75], [75-84] and [85-95].

The second graph shows the average number of women who had a MACE in the second period, ranging from 2031 to 2050. Here we see that age groups [65-75] and [75-84] are the ones with the highest percentages, albeit lower than in the first seven years. The relative number of MACEs in the age-groups [45-54], [55-65], [85-94] and 95+ has gone down quite a bit compared to years 2023-2030.

The third graph presents the same KPI for the last 20 years. The results of the first age groups are similar to the second period five. For the age groups [65-74] and [75-84] we see either a small increase or decrease per scenario from the second period. We see a big increase in the relative number for the last two age groups.

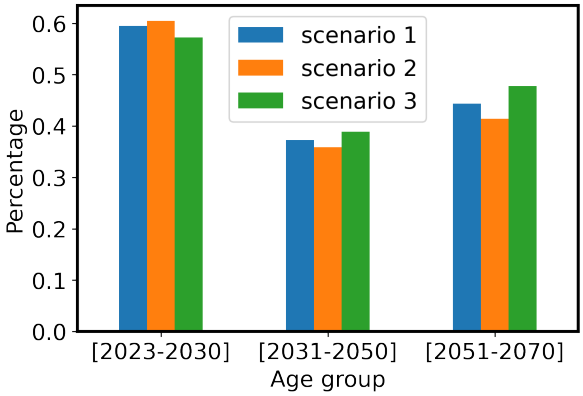

Figure 7.3: The average of the average percentages of women getting a MACE per year per age group per period.

For the last two periods, on overall, the third scenario had the most relative number of MACEs, but only by a small margin. This is shown in Figure 7.3. This figure shows the averages of the values used in Figure 7.2. It shows there are more events in the first seven years than in the subsequent periods. The most relative MACEs occur in the second scenario in the first seven years, whereas they occur in the third scenairo in the subsequent periods.

Figure 7.4 shows that the average age of women getting a MACE increases over the years. The graph clearly shows the average age increases over time, for all scenarios.

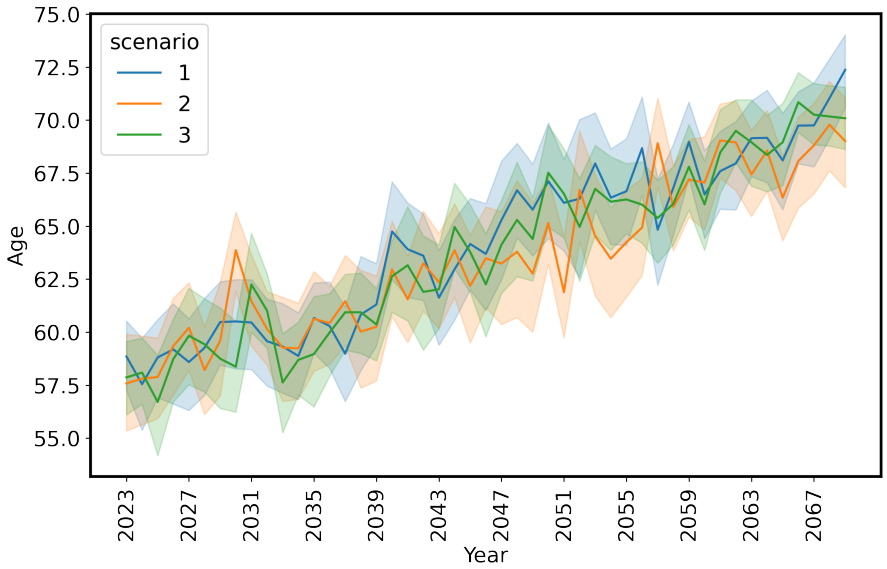

Figure 7.4: The average age of women getting a MACE in the base case over time.

The smoking behaviours in all scenarios for adolescents and adults is shown in Figure 7.5 and Figure 7.6 respectively. It clearly shows that more women smoke and start smoking in scenario 2 than in the other two scenarios. This is true for both adults as adolescents. For the remaining two scenarios, the emerging smoking behaviours of the virtual population are quite similar.

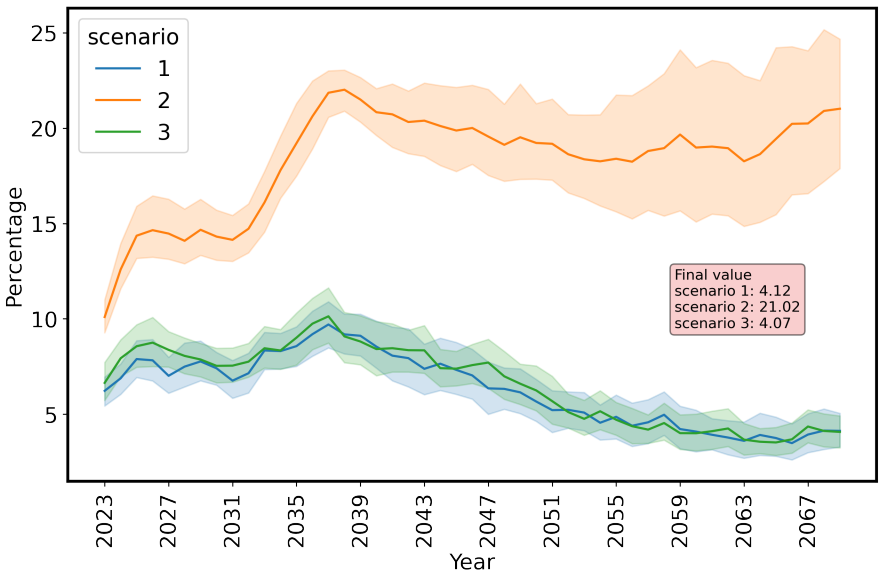

Figure 7.5: Percentage of adolescents smoking over time per scenario for the base case.

When comparing the final values of all scenarios in both Figures 7.5 and 7.6 it looks that there are relatively more adults smoking than adolescents. The trends for the adults are also appear less linear then the trends for the adolescents.

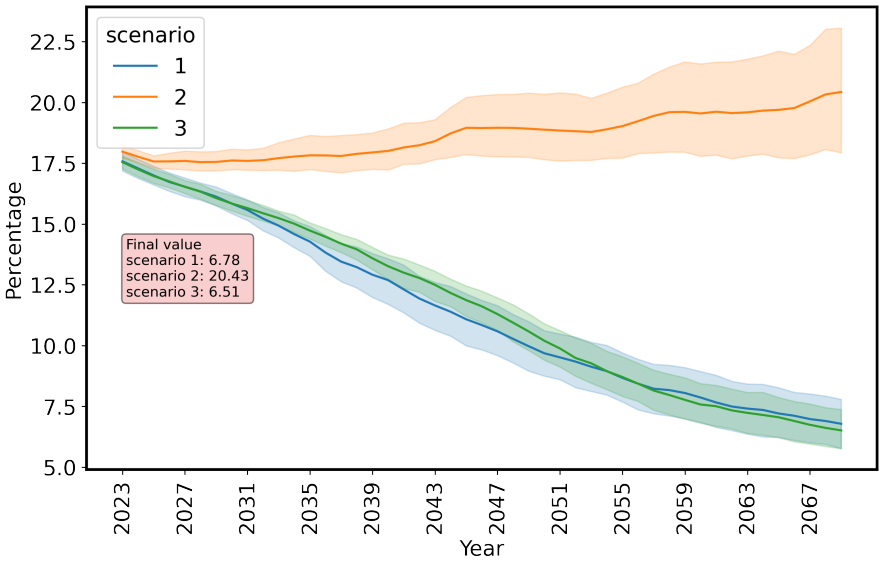

Figure 7.6: Percentage of adults smoking over time per scenario for the base case.

Finally, we present the percentage of women who were either overweight or obese in all three scenarios over time. The results are shown in Figure 7.7. Across the scenarios, we see quite similar results. For all periods, the age groups [25-65] and 65+ have the most overweight and obese women relatively. We also see that the percentage increase over time. In the first period the age group [12-17] has relatively the least amount of women with a BMI of 25 or higher. However, in the second and first period, which comprising the final 40 years of all simulations, this position is held by the age group [18-24].

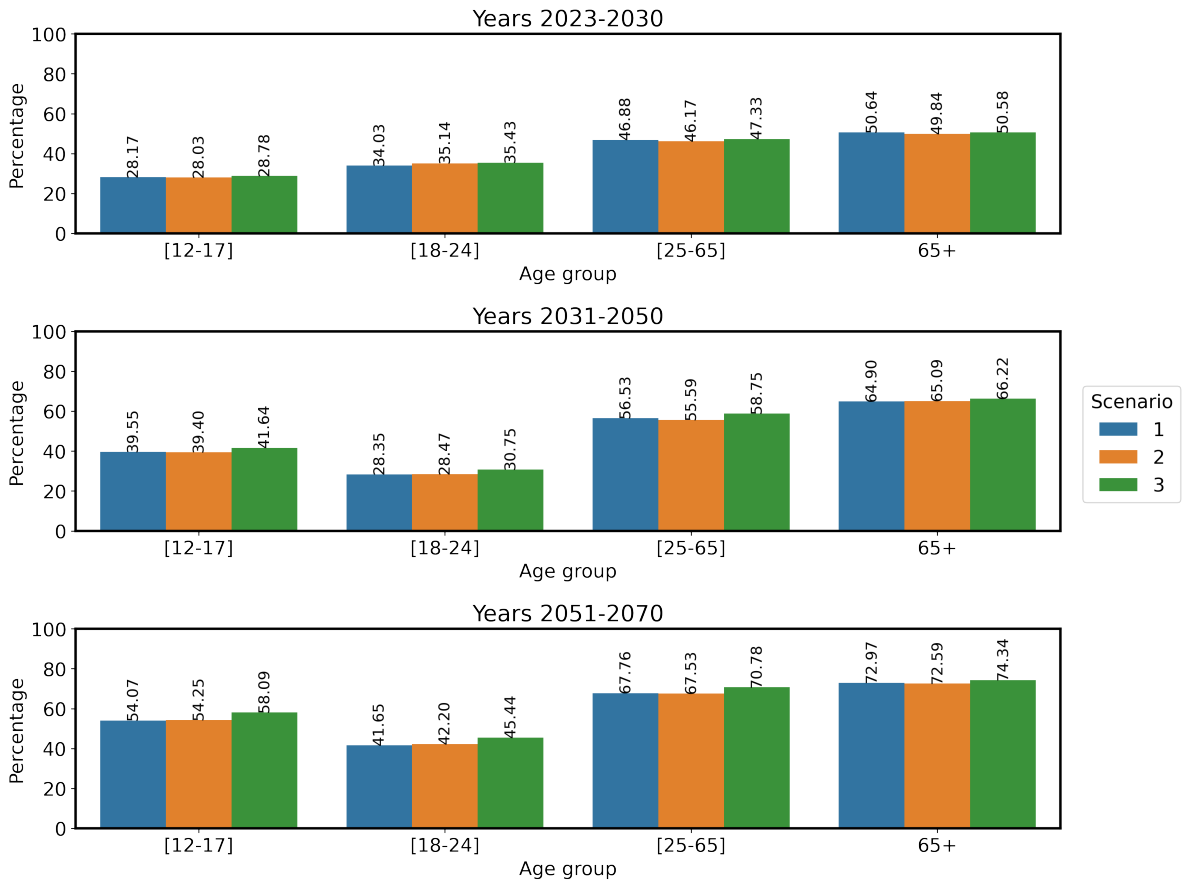

Figure 7.7: The average percentage of women who are either overweight or obese in the base case for all three scenarios per age group.

7.3. Interventions

In this section we show the effects of the interventions on the virtual population. The interventions have been described in Chapter 5. For convenience, we are also present them in Table 7.1. The *immediate* intervention has no variations, whereas the remaining three interventions have four or five alternative parametric variations. The variations are explained in Chapter 5. The *immediate* intervention is very different from the other interventions, as it is implemented immediately and is very intensive. It is also the only non-repeating intervention.

	School			Smoking			Targeted	
	Frequency	Duration	Reach	Frequency	Range of effectiveness	Duration	Number of people	Frequency
1	[1, 13, . . . , 589]	2	0.4	[1, 13, . . . , 589]	(-0.3, 0.1)	3	20	4
2	[1, 13, . . . , 589]	6	0.4	[1, 13, . . . , 589]	(-0.1, 0.1)	3	200	4
3	[1, 37, 73, . . . , 577]	5	0.9	[1, 13, . . . , 589]	(-0.1, 0.1)	1	200	1
4	[1, 7, 13, . . . , 595]	1	0.3	[1, 37, 73, . . . , 577]	(-0.1, 0.1)	6	400	4
5							400	1

Immediate: immediate reduction of the percentage of woman obese or overweight to 30%

Table 7.1: All interventions from Chapter 5 summarised

Using the regret score on the average number of MACE in the first 10 years, Figure 7.8 shows that the *immediate* intervention outperformed the other interventions in all scenarios. In fact, the impact of the other interventions on the scenarios was rather poor. The graphs for these can be seen in Appendix D. The second best performing intervention depends on the scenario. In scenario 3 where women are more susceptible to influence from their network, the *school* intervention seems to outperform the other types of interventions. In scenario 2 where women are less likely to stop smoking and more likely to start smoking, two variations of the *targeted* intervention are the second and third best performing interventions. in the base case, both a version of the *smoking* intervention and the *school* intervention do well. If the *immediate* intervention cannot be implemented, based on these results, it would probably be best to implement the *school 2* intervention given its performance in all three scenarios.

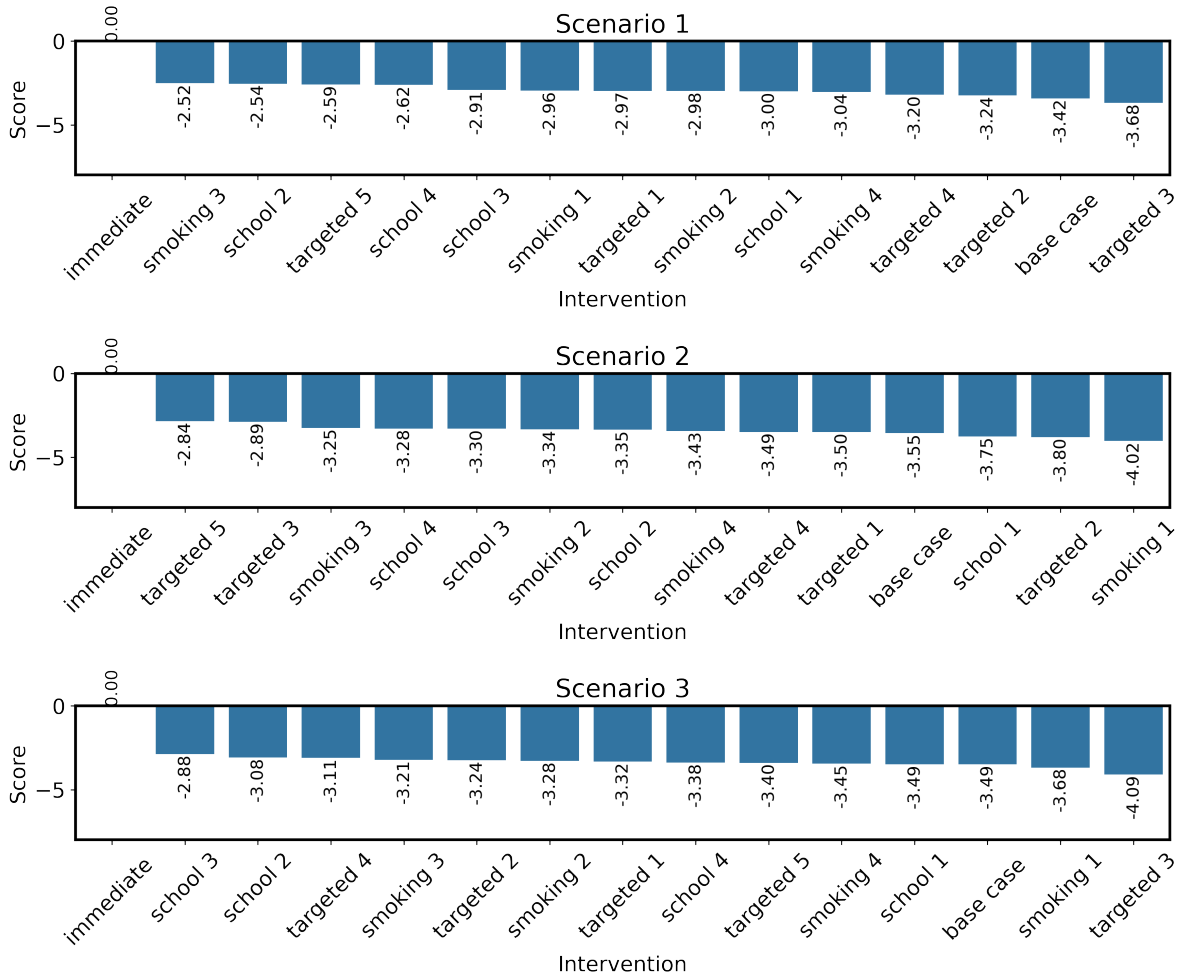

Figure 7.8: The regret KPI for the different interventions under different scenarios.

Interestingly, the *immediate* intervention only improves the situation in the first 30 years, after which the general behaviour of the female population will nullify its effect. This can be seen in Figures 7.9 and 7.10. Note that the bands around the interventions show the confidence interval. We see in Figures 7.9 and 7.10 that the average number of MACEs and the average age for both the base case and the *immediate* intervention converge to similar values. Since the KPI does not look at the preventable number of MACEs, but to the total number of MACEs, the figures somewhat hard to interpret. The intervention is implemented at the start of the run, meaning that a bigger proportion of the MACEs after implementation will be due to old age (and as such not preventable), opposed to other risk factors. Additionally, a proportional bigger segment of women will die due to old age. Both of these will be removed from the scheduler.

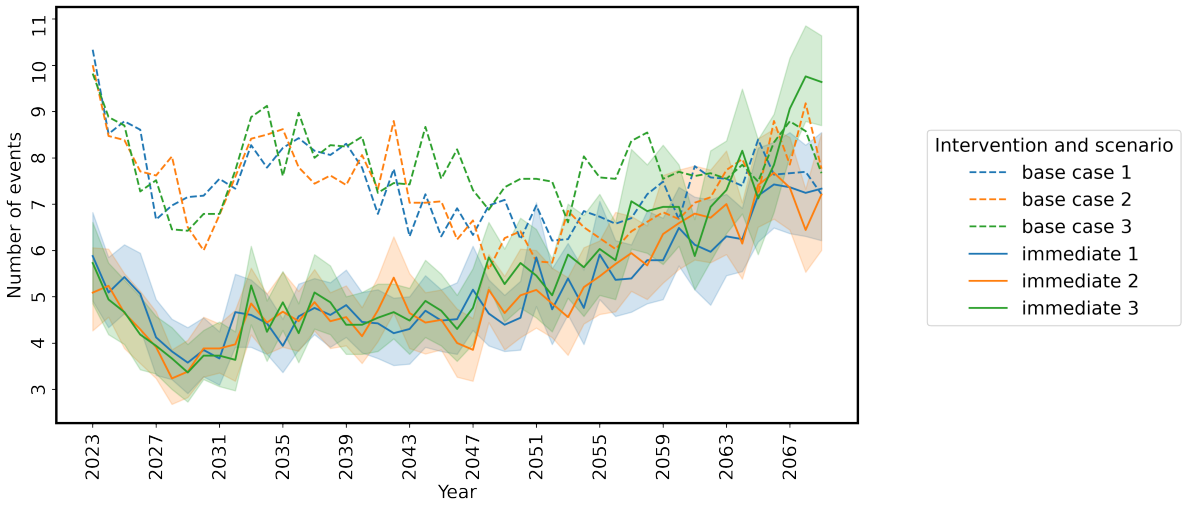

Figure 7.9: The average number of MACEs per year resulting from the *immediate* intervention.

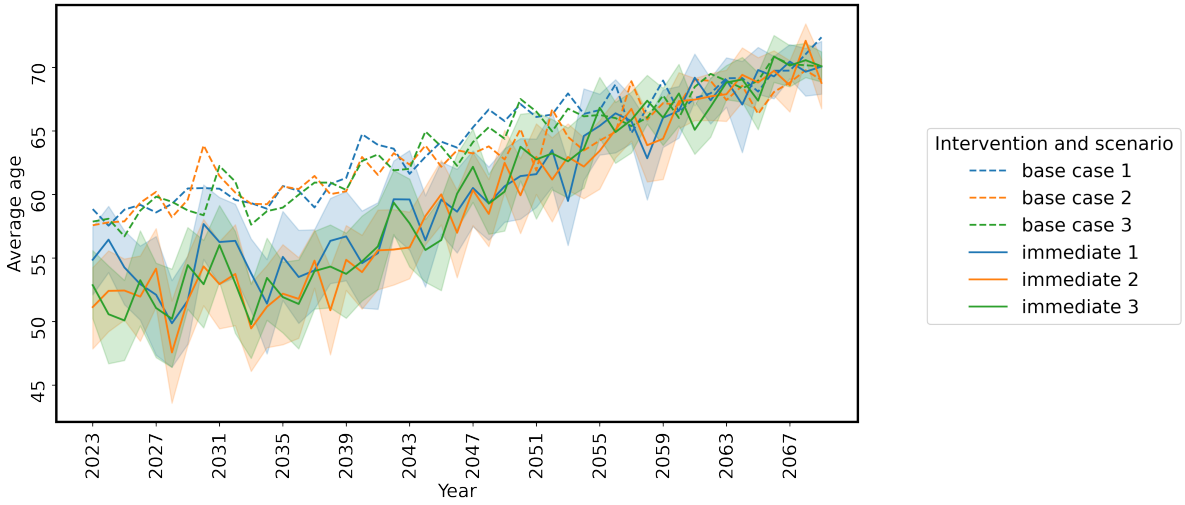

Figure 7.10: The average age of women getting a MACE resulting from the *immediate* intervention.

In Figure 7.11 we present the results from the base case and the results from the *immediate* intervention. The light colours represents the results from the base case, whereas the more saturated colours represent the results from the intervention. We can clearly see a decrease in the average age for the first 30 years, which seems mostly nullified in the last 20 years.

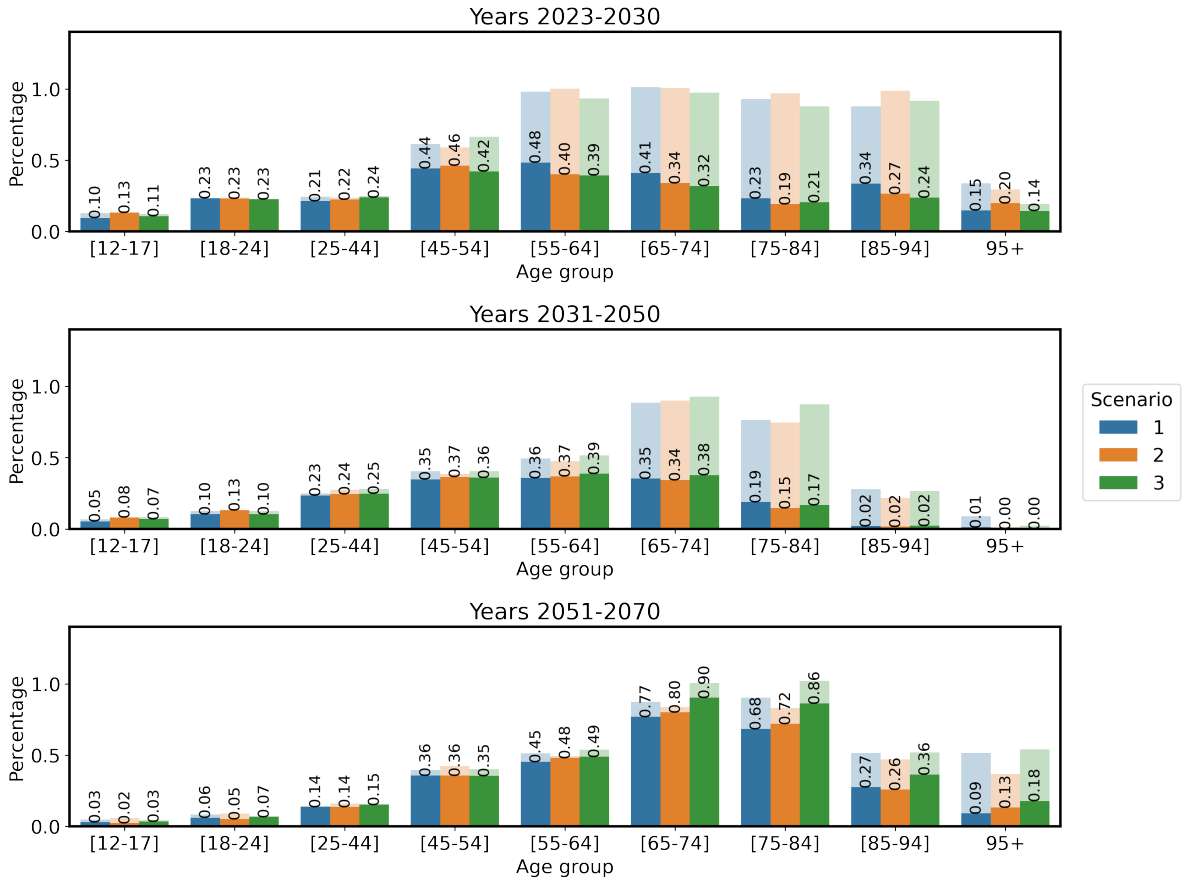

Figure 7.11: The average number of MACEs per year as a result from the *immediate* intervention.

The previous observation, of the immediate intervention being nullified, is also supported by the fact that the percentage of people who are either overweight or obese seems to improve for the first 30 years, after which we see it rise to the average of the base case. This is shown in Figure 7.12.

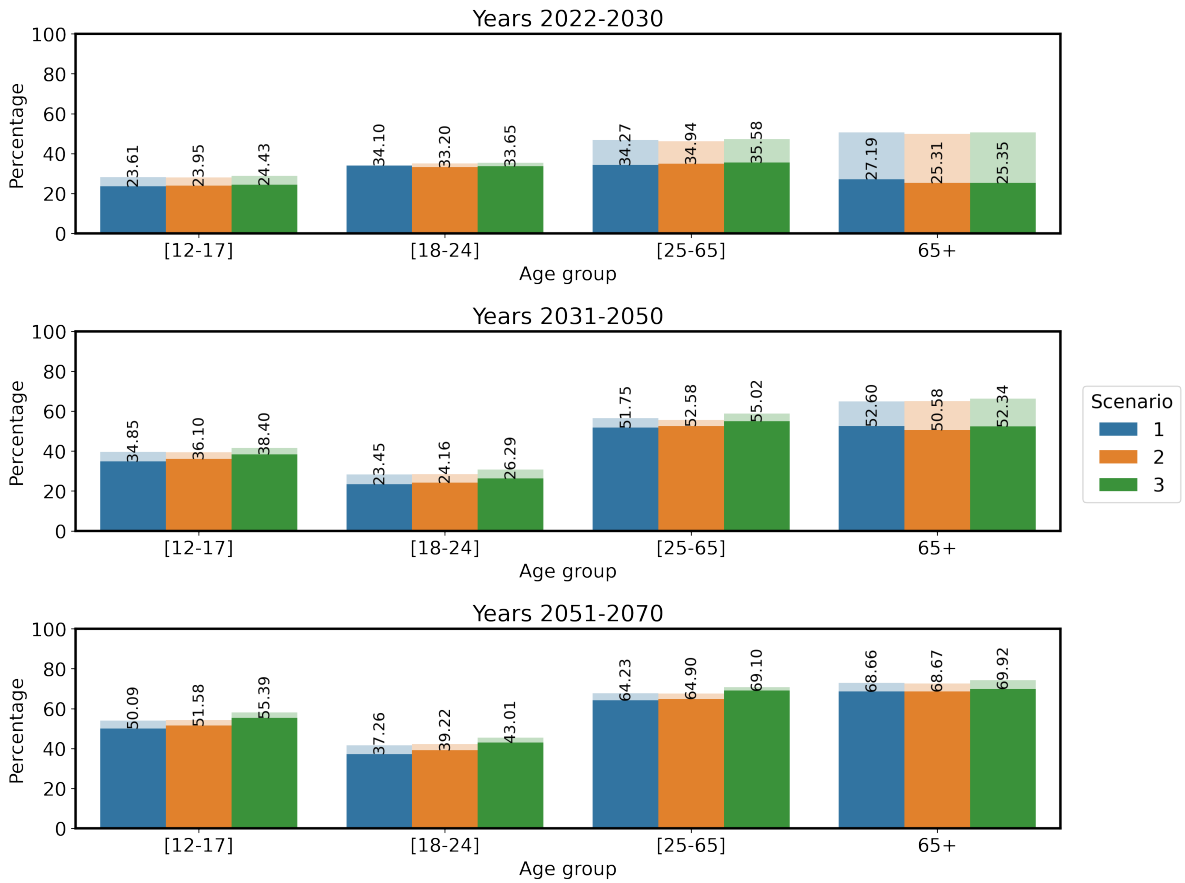

Figure 7.12: The percentage of people overweight or obese in the base case and under the *immediate* intervention for all scenarios.

More results for the *smoking*, *school* and *targeted* intervention can be found in Appendix D.

8 Discussion

This chapter presents the implications of the results to the sub-questions and the research question. The end-goal of this project was to explore screening and behavioural interventions to alleviate the cardiovascular burden among women in The Hague. All previous chapters worked up to reach that goal, whereas this chapter places the finding in the larger context. Additionally, we reflect on the approach, the assumptions, and the strengths and limitations of the model presented in this thesis.

8.1. Implications

The literature study that was conducted identified CVD risk factors, entry points, and their relationships. We identified many risk factors, but only a few useable entry points. Energy expenditure and intake are multi-purpose: they will not only reduce CVD risk but also reduce the risk of other risk factors. This is thus an exciting result, as targeting these entry points will significantly multiple risk factors.

The Fine and Gray model that we fitted on the ELAN and CBS dataset showed that age was the most dominant risk factor for a MACE. The second most-dominant risk factor was smoking. Age is not a modifiable factor, but given the knowledge that the population of The Hague is ageing, it is fair to say the number of women suffering a MACE event will increase. The Fine and Gray model also shows the danger of having multiple modifiable risk factors when younger.

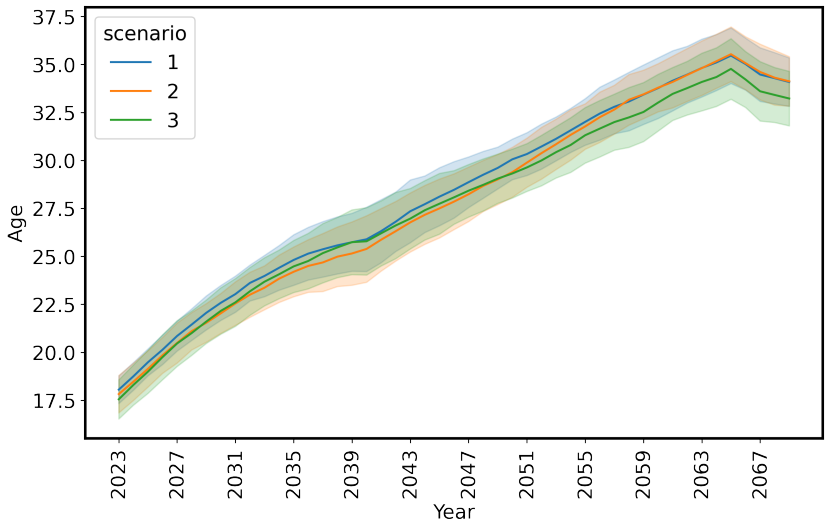

Figure 8.1: The percentage of the virtual population over 65 years old over time in the base case.

The data used as input was quite alarming already. Obesity and being overweight are already prevalent among women in The Hague, despite this being a major driver of cardiovascular risk. Being overweight and obese is also strongly associated with other risk factors (Mokdad et al., 2003).

The simulation results show that the number of MACEs among the female population of The Hague will increase. This is due to two reasons: First, the number of people with risk factors will increase.

Second, as shown in Figure 8.1, the population will age. The Figure shows the percentage of women aged 65 or older in the virtual population.

Under the assumptions we made, our model was too saturated with unhealthy behaviours for moderate policies to be effective. The effects of the moderate policies we implemented were negated by this. Essentially it showed it is already too late for The Hague to implement moderate policies, and more intensive interventions that target multiple behaviours are required.

8.2. Scientific contribution

The literature study that was performed revealed that risk assessment of CVD can still be improved, for the following reasons: 1) a multitude of risk factors, such as stress and depression, are understudied, and; 2) the relationships between all risk factors is still unclear. The question thus arises of how well the current method of CVD risk estimation is. After all, to reduce the total CVD burden long-term, we need to determine the impact of (preventative) treatment, which we can only do if we know what risk factors to target.

To the best of our knowledge, the model that was developed for this thesis included a lot of firsts. Up to our knowledge, we created the first agent-based health model that integrates a Fine and Gray model. Additionally, it is also the first of its kind to include multiple data models for the risk factors: fasting blood glucose, total cholesterol, and systolic blood pressure. This may be because we had access to a novel and rich dataset that allowed us to realise those models. Lastly, this model is the first of its kind to focus on women and that looks at women over their entire life.

There are several published studies of agent-based models that looked at cardiovascular health. Y. Li et al. (2014), Y. Li et al. (2018) use state charts as opposed to data models. They do however include risk factors such as diabetes, hypertension and high cholesterol. Agents transition from one state to another based on probabilities. They even remark that that is a limitation of their model, which is addressed in the model presented in this thesis. They also remark that their model is limited as there is no social interaction, which we did include in our model (Y. Li et al., 2016). Garney et al. (2022) also looks at the long-term outcomes of policies, and similarly concluded that the effect of policies is not significant enough. Multiple agent-based models have been developed that target health behaviours, but these just address part of the problem when it comes to CVD Tracy et al. (2018).

A couple discrete event simulation models and system dynamics models have been developed to assess the impact of interventions on the cardiovascular health profile of the simulated population (Arrospide et al., 2022; Homer et al., 2008; Homer et al., 2010; Yarnoff et al., 2021). However, most of the models are Markov or spreadsheet models (Breda et al., 2021; Lewsey et al., 2015; Saha et al., 2019; Salgado et al., 2019; World Health Organisation, 2019). All these models do not capture the interactions between agents, and sometimes do not even differentiate between men and women. They have compartmentalised the real-world issue and similar policies are shown to be more effective in their models. This may be due to the fact that they lack certain details, such as diabetes, hypertension, and high cholesterol.

This piece of work includes a simulation model that integrates knowledge from different disciplines, and as such, was able to synthesise multiple research methods into one new method. As such, it can be seen as a “boundary object” (Leigh Star, 2010): it can aid interdisciplinary participation as it can further enhance communication between groups of people that lack a common knowledge base. It was not used like that in this thesis, but it became clear from the interactions between all members from the graduation committee.

8.3. Societal contributions

Since energy expenditure and caloric intake are at the root of a lot of risk factors. We propose interventions should be aimed at these entry points. However, interventions to improve energy expenditure and caloric intake will likely take more time to affect the number of MACEs, as their effect is gradual. We also propose that the national and local government keeps trying to reduce the number of smokers in The Hague, as the Fine and Gray model shows that that risk factor is dominant.

The current 10-year risk estimation used in society is suboptimal. This is displayed in Figure 7.1, where we see that the risk is substantially higher for younger people if they have multiple risk factors. However, the current guide only assesses women age 45 and older (Nederlands Huisartsen Genootschap, 2019). It is therefore wise to update this assessment to prevent MACEs.

Thus, our findings indicate that certain subsets of the population may be overlooked and it is clear we need to act fast and we need to act now. This work did not look at interventions in-depth that could realise this change. It is likely a combination of interventions is necessary to achieve change. These interventions would likely include parties from all sectors, such as: governments, health professionals, supermarkets, and take-out restaurants. It is going to be complicated to realise this, given the high degree of individualism in the Netherlands (Hofstede Insights, 2022). The UK has a similar individualism score on Hofstede's model, and their people vilified the government when it became too overbearing (Theis & White, 2021).

8.4. Strengths

As presented in this thesis, ABMs can help to address complex health problems in public health. However, their potential is still largely untapped. One of the strengths of this work is that it shows how knowledge and data from different disciplines can be combined into an agent-based model to explore different interventions targeting cardiovascular diseases among women in The Hague. We have combined data and models from health and population studies, and theories from the fields of social network and behaviour studies. To our knowledge, this study is one of the first to develop a multi-disciplined model of this magnitude.

The model shows the long-term benefits, the so-called "legacy effect", of behavioural interventions, which has been largely understudied (Viñas Esmel et al., 2020). The legacy effect of these kinds of interventions has been understudied since it is almost impossible to keep track of people's health conditions in a controlled environment long-term. A virtual environment is thus a necessary tool for researchers and policy-makers to, on the one hand, identify multiple trajectories for the population of The Hague with or without interventions in a relatively short period, and on the other hand, explore the fundamental underlying structures that give rise to phenomenon we see in real life. In the case of our model, the latter refers to the influence of a woman's social circle on her health behaviours.

Not only can the model gauge the effect of multiple structural and numeric assumptions on the virtual population, while also including uncertainties. It can also view the effects of assumptions, scenarios and interventions that can be investigated at different granularities. The model presented in this work looks at both characteristics of the entire female population in The Hague, but also at specific groups. One intervention even attempts to dynamically identify which community should be targeted when resources are limited. The model could also easily be adapted to look at the attributes of specific agents.

8.5. Limitations

We acknowledge that even this work has limitations. Several methodological and theoretical limitations need to be accounted for.

Regarding methodological scenarios, a vast range of uncertainties and scenarios have not been (sufficiently) included in the model due to a lack of time or data. Some of these were identified during the literature studies, such as alcohol consumption, and socio-economic status. On the former, the literature could not find consensus, and the latter was only included rather superficially Others stem more from common sense, such as the effect of marriage on the composition and the cardinality of a female's social network (J. J. Rözer et al., 2015).

Unfortunately, we are unable to say how truly valid the results are, as certain uncertainties have been largely excluded, which reduces the diagnostic capabilities of the model. After all, interventions have not been subjected to all factors that may amplify or reduce their effect. The list of uncertainties includes but is not limited to possible future trajectories regarding environmental pollution, climate change and population size and composition, and white swans such as pandemics. It has been observed that higher temperatures increase the risk of getting a MACE (Huynen et al., 2001; Lin et al., 2009). The model only accounts for one population trajectory, even though multiple are imaginable. Similarly, if a pandemic were to happen again, measures may affect the behaviours and social networks of women this. During the COVID-19 pandemic the measures taken weakened social networks. As a result, more people experienced loneliness, anxiety, and depression (Bansal, 2020; Jaspal & Breakwell, 2022).

The model relies heavily on the Body Mass Index and Wishnofskys Rule. It should be said that BMI does not distinguish between lean and fat mass, and Wishnofsky's rule has been deemed too simplistic by researchers such as Thomas et al. (2014). However, due to data availability and the lack of better alternatives, we had to resort to using these two concepts. In this model, BMI may carry too much

weight, as all GLMs depend on it, and the results are fed into the Fine and Gray model. Also, due to the lack of data, at initialisation, the model assumes all ethnic groups have similar distributions of BMI.

The social networks that are generated and maintained in the model do not take the socio-economic status of women into account, despite there being evidence this may be relevant. In fact, the entire rule set that determines whether two women will befriend each other is mostly based on assumptions due to a lack of data. This is similar to the behaviours of women regarding smoking and their susceptibility to influence from their social network. We simply do not have the data and were just forced to resort to "reverse engineer" a hypothetical mechanism to achieve the behaviours we see in the real world. Additionally, the cuts used for the income groups are subpar. We used the cuts used by Centraal Bureau voor de Statistiek (2019a) and as a result the biggest income groups only encompass a small percentage of people, whereas the lowest income group encompasses a big group of people as shown in Table C.10. This has affected the Fine and Gray model.

The model is also inaccurate in the way medication usage was implemented. Ideally, women are prescribed medication as a result of their medical risk factors. However, this relationship is twisted in the model, due to the way data was processed. Essentially, women start taking medication to increase their risk factors. This was a methodological mistake.

Finally, our KPI only showed the total health burden and did not show the number of MACEs that could have been prevented. We did not implement a method to investigate cost-effectiveness, as there was simply too little data on both the costs of interventions and on the (continuous) costs for a woman who got a MACE.

8.6. Directions and recommendations for researchers and modellers

During this project, a lot of lessons were learned to advance the multidisciplinary field of population-based simulations to inform CVD policies. We expand on these lessons in this section, starting with suggestions for future models and ending with suggestions for potential research.

8.6.1. CVD and other non-infectious disease models

Future models that take into account the social network may consider developing more intricate interaction models. The model implemented in this model did not use the socio-economic status (SES) as an attribute women take into consideration when befriending other women. SES can function as a proxy for education and occupational status and is thus an interesting attribute to include. For instance, Damen et al. (2021) explain that non-Western ethnic minorities have a higher chance of befriending Dutch people if they have a higher SES. Dutch women tend to have fewer friends of a different ethnicity if they have a high SES.

Additionally, major events in a woman's life have been known to affect her network, such as pregnancy and marriage. The composition of the social network of women changes post-pregnancy, they lose touch with some friends but gain contact with neighbours (J. Rözer et al., 2017). Similarly, it is argued that having children increases family bonds (J. Rözer et al., 2016).

It may also be interesting to allow the agents to reason, by using, for instance, a behavioural model such as the belief-desire-intention (BDI) model, the theory of planned behaviour (TPB), and/or the health belief model (HBM). This is especially interesting as it has been observed that women with a moderate risk of developing CVDs are reluctant to take preventive actions. They consider themselves healthy (Kotseva et al., 2020).

Since it has been shown communities tend to be echo chambers of health behaviours (Evans et al., 2016), it is interesting to explore more interventions that these groups to shift group-level norms and to perpetuate healthier behavioural norms. To realise this, it may be interesting to use an existing network that meets the small-world attributes. That would mean that there would be far more cliques, as compared to the network created by this model.

Concerns have been raised that preventive cardiovascular programmes may increase health inequalities. This is due to a phenomenon called "intervention generated inequality" (Lorenc et al., 2013), which claims that socially advantaged groups are more likely to be reached by screening efforts. There is however little evidence backing this claim and no data or theory about women in specific. Agent-based modelling could be used to explore under which conditions and to which extent this claim is valid, which is especially interesting given that the Netherlands wants to move to more individualistic

preventive policies (Tweede Kamer der Staten-Generaal, 2011).

8.6.2. Population studies, research, and data

For this thesis, we had the luxury of linking potent datasets, which allowed to fill some data gaps. We were also able to augment the individual health and population data with high-quality disaggregations of open-source population data. However, we also identified gaps in data that we feel could guide future data collection efforts. Here we outline priorities and considerations to guide efforts to fill these data gaps that will improve future public health models.

First of all, because lifestyle factors are not components of traditional cardiac risk scores for primary prevention risk stratification, recognizing and clarifying more of these factors may further guide CVD risk assessment and targeted preventative measures. In our model, we used the approach of translating a small subset of behaviours to numerical effects on food intake and exercise, which resulted in one BMI value, which was used in conjunction with other factors for other additional calculations. We did however identify more potential behaviours of interest in the literature study, that we could not account for properly due to a lack of data and/or knowledge, such as alcohol consumption and genetics and the interplay between different factors. Future research could, for example, show that the current model includes covariant variables, which would affect its diagnostic power.

Secondly, it would be valuable to explore the extent to which changes in health behaviours are prompted by one's social circle and/or external factors, and the extent of autonomy women have when making these choices, especially relating to age, ethnicity, and perhaps other factors, and how to translate these translate into effects on the female body. Special consideration should be put into the long-term effects of these choices. There are a couple of studies that look at a somewhat granular level of health behaviours of women, but the "bridge" connecting these studies to usable data for a simulation is usually lacking. As a result, the bridge connecting these kinds of behavioural datasets to biological effects is based on assumptions. An example of a valuable study that needs such a bridge is the work from Cornelisse-Vermaat and Maassen van den Brink (2007), which could have been used for effects on lifestyle variables and socioeconomic status on overweight among native Dutch and immigrants in NL.

Similarly, there is little data on the (long-term) effects of policies. In the experiments executed in this work, the values that reflect the effect of policies are assumptions. This is problematic for two reasons. First, preventative health policies do not have numerical end goals. We were unable to find any intervention with a clear goal. Policies are implemented, but the desired outcomes are always vague. Either the population has to "just" reduce the population's overall risk, or there has to be "some" reduction of a certain observable behaviour. This makes it impossible to conduct a cost-benefit analysis and to argue why certain policies are implemented. Secondly, to truly realise the big picture of the underlying behavioural and biological mechanisms that are being exploited by policies, and how these may be amplified or nullified by external factors and social factors, we need to have some hypothesis or working theory on how interventions connect to groups and/or individuals.

New prospective population studies are necessary to establish the true cardiovascular risk profiles of women in a changing society. They could be determined by doing surveys of the female population of The Hague, and by conducting multidisciplinary research.

8.7. Recommendations for policy-makers

The picture painted by this research showed we need to act powerfully and quickly. The longer we wait, the worse the outcome will be. Fortunately, we do believe most women of The Hague and the local government are on the same wavelength. Both are aligned in the sense that they prioritise health, and that the problem is primarily in how to reach women and prevent women from falling back into bad health habits.

Interventions focusing on self-management are more effective than passive interventions, meaning intervention through education and information sharing (Sakakibara et al., 2017). This is probably because the individual feels empowered to manage their lifestyle. It may therefore be constructive to establish skills such as goal-setting, decision making, and self-monitoring (Lorig et al., 2005; Michie et al., 2009).

CVD-related health policies should try to target one or more of these risk factors to avert CVD. Emphasis should be placed on the risk factors that contribute most to the risk of CVD within the target

group. This includes food intake, exercise, and smoking. It may be more difficult to address food intake and exercise, as everyone knows smoking is bad, whether eating and being sedentary are not inherently bad.

Regarding smoking, it would be wise to continue monitoring and studying both the health effects of vaping, and whether the e-cigarette is an actual gateway to smoking or not (Chatterjee et al., 2018; Prieger, 2020). Smoking is such a dominant risk factor, we need to be on top of the popularity of vape pens.

Based on the literature study we conducted, and the behaviours that emerged from the model, we first suggest that policy-makers change their rhetoric and perspective. Food intake and energy expenditure are not just the result of an individual choice. Women's health is a cumulative consequence of behaviours affected by their social network and environment.

It is advisable to give women a certain autonomy over their CVD progression. Especially considering we do not have access to the resources to not explore this option. However, our research showed that a woman's autonomy cannot be excluded from the social context. If we want to change behaviours, we also need to look at social and external factors of women. This will not only improve the modifiable risk factors determining their likelihood of getting a MACE, it will also decrease the likelihood of getting other non-communicable diseases

If we want to slow down the increase in the healthcare burden or even reduce the healthcare burden, screening and behavioural interventions can prove to be extremely valuable. The interventions that proved to be most successful, were the ones that were repeated most frequently or had the longest lasting effects.

We are well aware the Netherlands is heading to a situation where there will not be enough personnel in healthcare to support the population (Nederlandse Omroep Stichting Nieuws, n.d.). So to relieve the health care system, we have to make use of modern screening methods, such as metabolic carts, and by informing and supporting communities. We also have to acknowledge the importance of networks as behaviours can spread within social networks.

9 Conclusion

In this chapter, we first answer all sub-questions. Finally, we answer the research question.

Sub-question 1. What are the social and biological risk factors to reduce the health burden of CVD in women?

Based on the literature study in Chapter 3, the data models described in Appendix C, and the conversations we have had with the experts at LUMC, we deduced that aside from traditional risk factors: age, lipid metabolism, blood pressure, and smoking (Nederlands Huisartsen Genootschap, 2019), we also needed to include additional ones. We identified many risk factors, but we decided to limit ourselves to fasting blood glucose, ethnicity, pregnancy complications, caloric intake, energy expenditure, genetics, socioeconomic status, and smoking history.

We found that the scientific community is often not aligned on the effect or the magnitude of the effect of a certain risk factor. Additionally, the intricacies of the interactions between the risk factors are complex and should be further examined.

We also observed that a woman's health behaviours are heavily influenced by her social network. Smoking and eating are individual behaviours, but it is unjust to not place them in the broader social context. Persistence in (un)healthy behaviours may be a response to social circumstances, in which case, it may be promising to address the social network of a woman, as opposed to victim blaming her choices.

Sub-question 2. What are the entry points to reduce the health burden of CVD in women?

The modifiable risk factors of the risk factors identified for sub-question 1 are the ones that should be targeted by interventions, namely smoking, energy expenditure, and caloric intake. Additional risk factors that are interesting to explore are alcohol consumption and stress management. Smoking, energy expenditure, and caloric intake are both at the root of other risk factors. Once a woman is able to sustain healthy exercise, diet, and smoking habits, her body will find achieve healthy homeostasis. At that point, her risk of a first-ever MACE is only determined by the non-modifiable risk factors, such as age, ethnicity, and pregnancy complications.

Sub-question 3. How can health-related regression models be integrated into healthcare simulation modeling?

In order to answer sub-question 4 and the research question we realised we needed to find a way to harmonise individual health data (of women), population studies, social network studies, and behaviour studies. In order to incorporate an aggregated version of the health data in the agent-based model, we developed three generalised linear models and one Fine and Gray model that were integrated into the

agent-based model as separate modules. The generalised linear models update the total cholesterol, fasting blood glucose and blood pressure attributes every step, whereas the Fine and Gray model determines the 10-year first-ever MACE risk.

These data models also lead to additional findings, such as the importance of comorbidities when assessing a woman's risk of a first-ever MACE.

The multidisciplinary model itself proved to be a useful tool to investigate the hypothesis that was developed to answer the main research question. The model combined health, social network and behavioural modules elegantly, and, thus, led to new and useful insights that can aid both decision-makers and researchers. Additionally, this model can now be used as a "boundary object": a tool to cross the language barrier between multiple disciplines.

Sub-question 4. What is a plausible future regarding cardiovascular diseases in women in the Hague in 50 years?

To answer the fourth sub-question, we ran the model for 50 years, and unfortunately, it painted a rather grim picture. The overall health of women in The Hague will decline and there will be an increase in the number of women getting a MACE event, and thus an increase in the prevalence of CVD.

There are two reasons for the negative trajectories painted by the model in Chapter 7. Firstly, the population of The Hague is ageing. When developing the Fine and Gray model, as explained in Chapter 6, we found that age is the most dominant risk factor regarding the first-ever risk of a MACE for a women. Secondly, without interventions, the population will propagate unhealthy diet and exercise behaviours, which will affect additional risk factors negatively.

Research Question. How can behavioural interventions decrease the healthcare burden of cardiovascular diseases among women in The Hague?

The interventions we tested were based on a hypothesis derived from the findings from the literature study. The hypothesis was as follows:

How can recurring interventions targeting diet, exercise or smoking behaviours decrease the healthcare burden of cardiovascular diseases among women in The Hague?

The hypothesis delineates the scope of the experiments. We systematically tested multiple interventions exploiting the entry points identified for sub-question 2 fitting this hypothesis, and also included an intervention that was **not** repeating but very intensive.

The results in Chapter 7 show that our formulation for the health issue is rather robust and resilient. It is robust as three out of four interventions hardly affected its course, and it is resilient as it bounced back after the impact of the *immediate* intervention. The *immediate* intervention did prove to be effective, but only for a limited period of time. The *immediate* intervention is also unrealistic to implement. There is no way to change the health behaviours of women rigorously and swiftly without receiving a lot of backlash.

If the formulation is true to the real world, then the results are a reason for concern. They indicate we may be past the point of no return. We should have intervened more rigorously in years gone by. With the benefit of hindsight, maybe this could have been avoided. However, this does not mean there is nothing we can do now. The model has clear limitations, as it omits certain complexities, meaning that there may be more room to improve the future.

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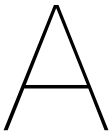

Assumptions

In this chapter we list all the assumptions we have made.

- We assume the age distribution for the general public in the Netherlands is true for each ethnicity.
- We assume the number of women that suffer from being overweight or obese are equal for all ethnicities
- Women stop growing at age 21
- The intensity of a woman's exercise programme depends on her age
- Women do not move out of the Hague, but women do move into the Hague
- We assume a population trajectory, both in the actual number of women, and the composition of the future population of the Hague
- We assume a numeric range a woman's desire to smoke has to fall between for her to start smoking and stop smoking
- We assume how susceptible women are to influences from their network

B

Sensitivity Analysis

In this Appendix we show how we performed the sensitivity analyses and we discuss the results of said analyses. The sensitivity analyses show how vulnerable the model is to parametric and structural changes. The sensitivity analyses deal with certain parametric and structural uncertainties that are explained in the Chapter 6. The results of the global sensitivity analysis are described in Chapter 6 as well. The results of the local sensitivity analyses are described here.

B.1. Uncertainties

B.2. Local sensitivity analyses

We also conducted a local analysis, to see the effect when we change one uncertainty at a time. First, we show the results of variations over the parametric space for the parametric uncertainties. Then, we show the effect of turning the structural uncertainties on or off. Note that we show the effect over the entire simulation run.

B.2.1. Numerical

For narrative clarity, we only show a subset of variations of the input space for each numeric uncertainty.

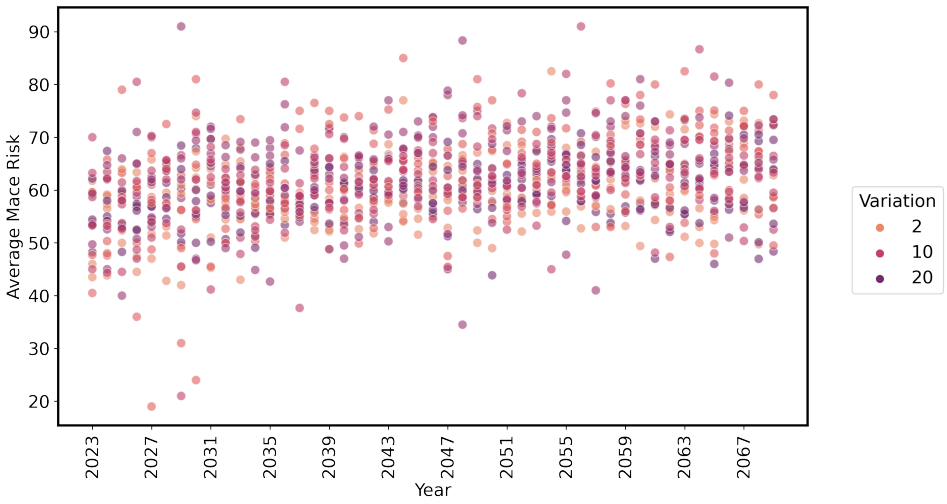

Figure B.1: The effect of different magnitudes of tolerability of age differences in a woman's friends group on the average MACE risk over time..

Figure B.1 shows the results for the tolerability of age differences. The legend shows the three variations. In the first variation, women will only befriend women when the difference between age is equal to 2 or less. For the second variation, the maximum acceptable difference equals 10, and for the third, the maximum acceptable difference equals 20. The range of outcomes is bigger in the first 10 years. After that, the KPI seems to converge, regardless of the variation used.

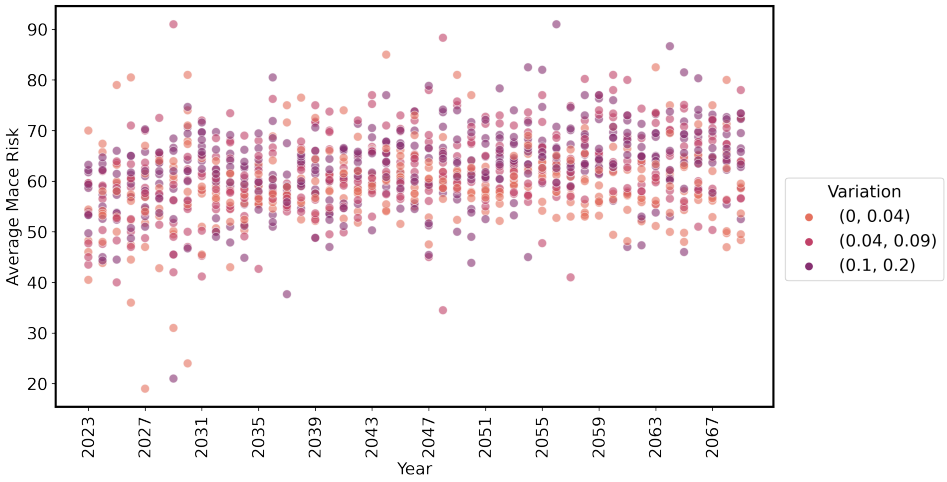

Figure B.2: The effect of different magnitudes of tolerability of women with different BMIs in a woman's friend group on the average MACE risk over time.

In Figure B.2 we present the results when we vary the ranges of tolerability regarding female friends with different BMIs. The variations go from the least accepting to more accepting. The KPI varies most when women are less willing to befriend women with a different BMI. The model is more susceptible at the start of the simulation.

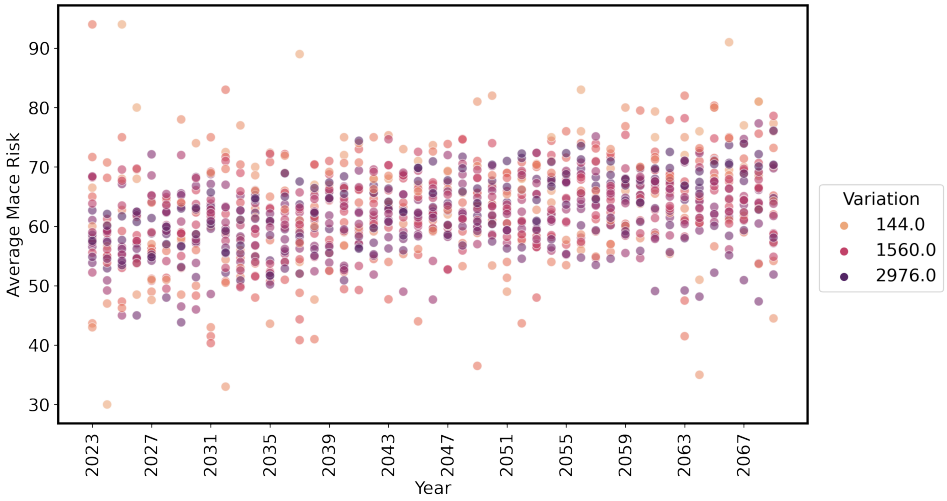

Figure B.3: The effect of different number of agents on the average MACE risk over time..

The effect of the different initial number of agents is shown in Figure B.3. The smaller the number of agents, the more variety we see in the KPI We do not see much difference between the variation 1569 and 2976. The average MACE risk at the start of the run varies between 20% and 90% in the first variation, whereas this band is considerably smaller for the 2976 variation.

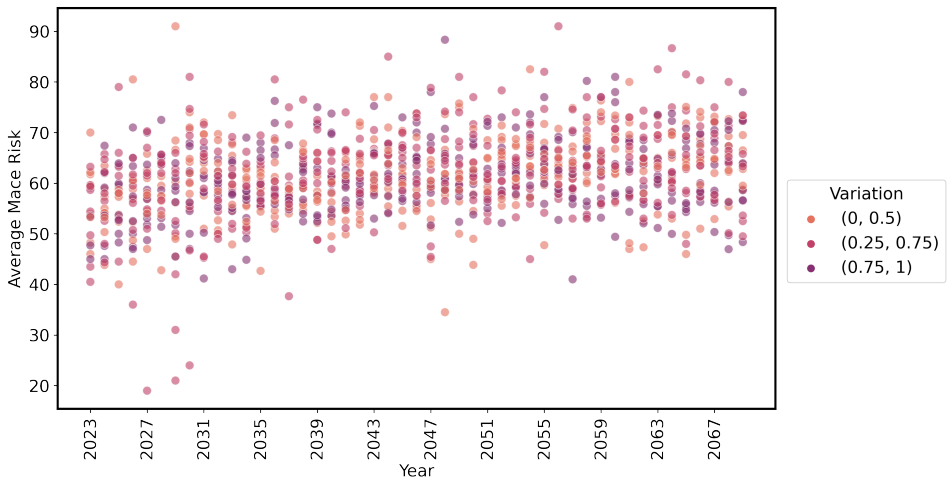

Figure B.4: The effect of numerical changes to susceptibility on the average MACE risk over time.

We also experimented with different ranges for susceptibility, namely (0, 0.5), (0.25, (0.75) and (0.75, 1). Figure B.4 shows the result. The differences between the three variations appear to be small, except in the first 10 years. The main band for all three seem to be the same.

B.2.2. Structural

To test the effect of certain modules in isolation, we simply ran experiments with the module turned on and experiments with the module turned off. The seed was chosen at random for each experiment. The results are displayed in the figures below.

Figure B.5: The effect the intention of weight loss module has on the average MACE risk over time.

Figure B.5 shows the result when the Intention module is turned on and off. The Intention module determines when and to what extent women may want to lose weight based on external factors. The main bands are comparable, but there are more outliers when the module is turned on. The model seems to be more sensitive at the start when the module is turned on.

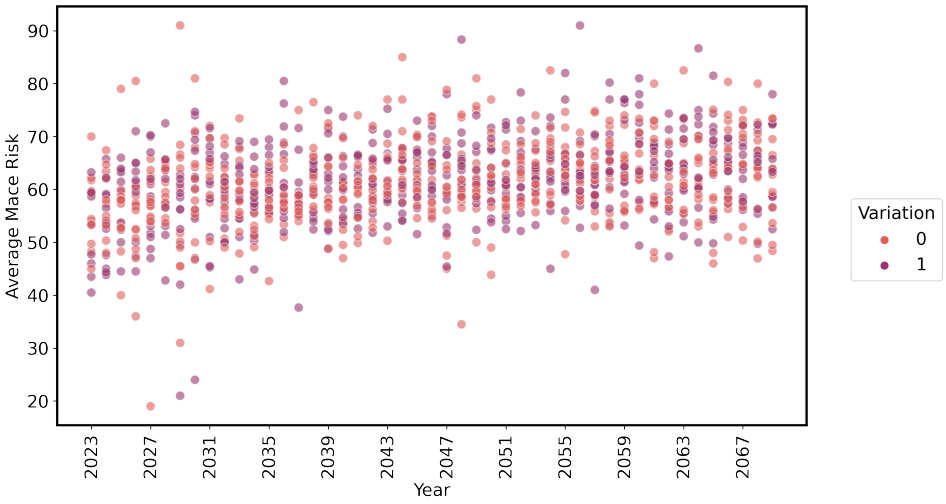

Figure B.6: The effect the population growth module has on the average MACE risk over time.

Finally, we look at the effect of the Immigration module. Yearly, the model looks at the difference between the actual population size and the projected population size. The latter is an input variable, that is scaled based on the number of agents the model is initiated with. Note that there are births in the model, and that the composition of the agents that migrate to the Hague is the same as the composition that the model is initiated with. Turning this module on or off does not really seem to impact the average MACE risk over time, although there are more outliers in the first 15 years.

C
Modules

This Appendix describes the details of some of the modules described in Chapter 4.

C.1. Growth formulas

The growth module enables to grow in height until the age of 21. The target height, as used in Equation 4.4, is different for each ethnicity. The equations are derived from TNO (2010). Figures C.1, **??**, C.3 and C.4 show the growth equations for the Dutch, Turkish, Moroccan and Hindustan ethnicity respectively. The standard deviations come from TNO (2010) as well. They are 6.3, 6.4, 6.5 and 5.9 for the Dutch ethnicity, Turkish ethnicity, Moroccan ethnicity and Hindustan ethnicity respectively. In the figures the pink markers are the data points and the black line is the fitted equation.

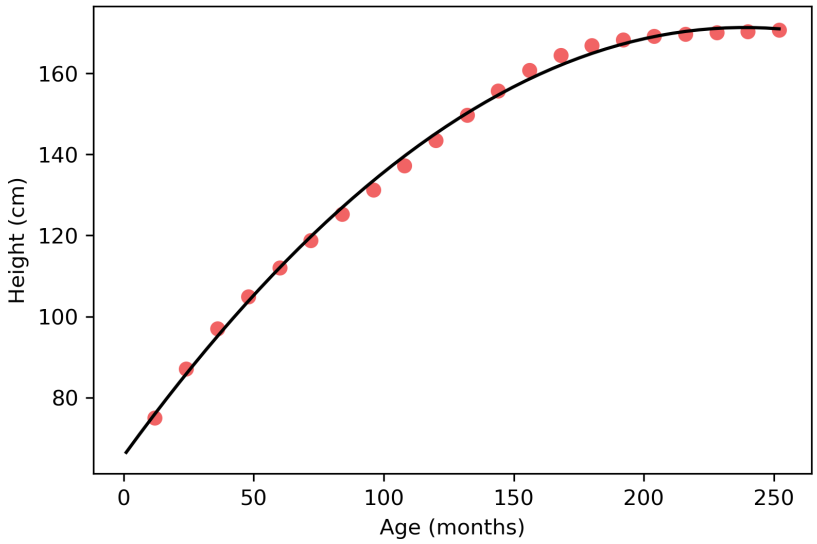

Figure C.1: Function for growth formula for women with Dutch ethnicity. The pink markers are the data points and the black line is the fitted equation: $-0.001855 \times x^2 + 0.886x + 65.57$ where x is the age in month.

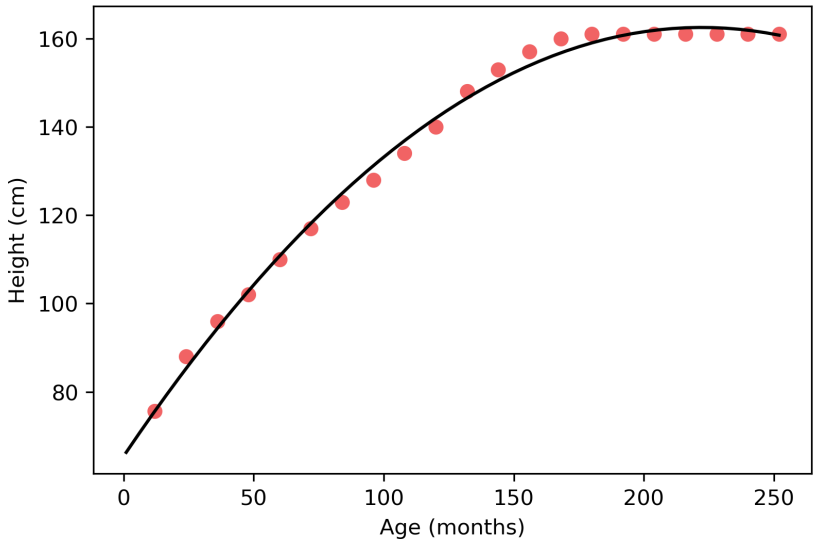

Figure C.2: Function for growth formula for women with Turkish ethnicity. The pink markers are the data points and the black line is the fitted equation: $-0.001966 \times x^2 + 0.8738x + 65.43$ where x is the age in month.

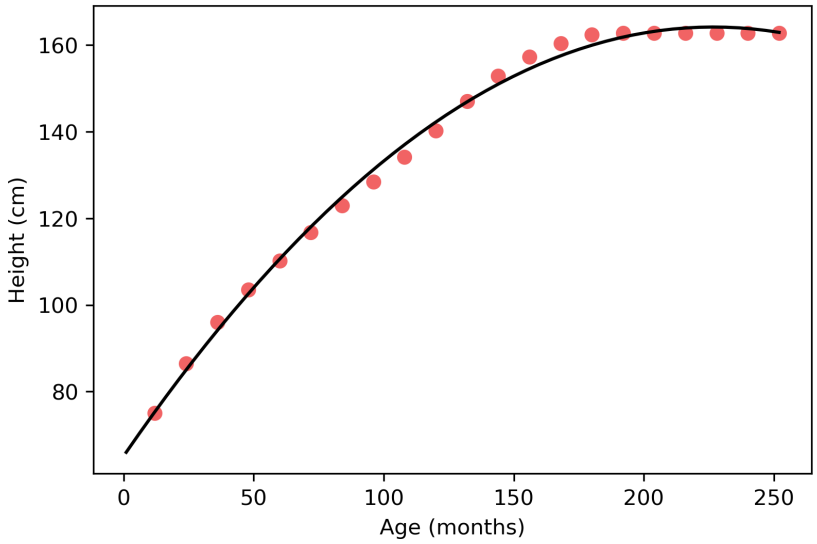

Figure C.3: Function for growth formula for women with Moroccan ethnicity. The pink markers are the data points and the black line is the fitted equation: $-0.001927 \times x^2 + 0.8737x + 65.11$ where x is the age in month

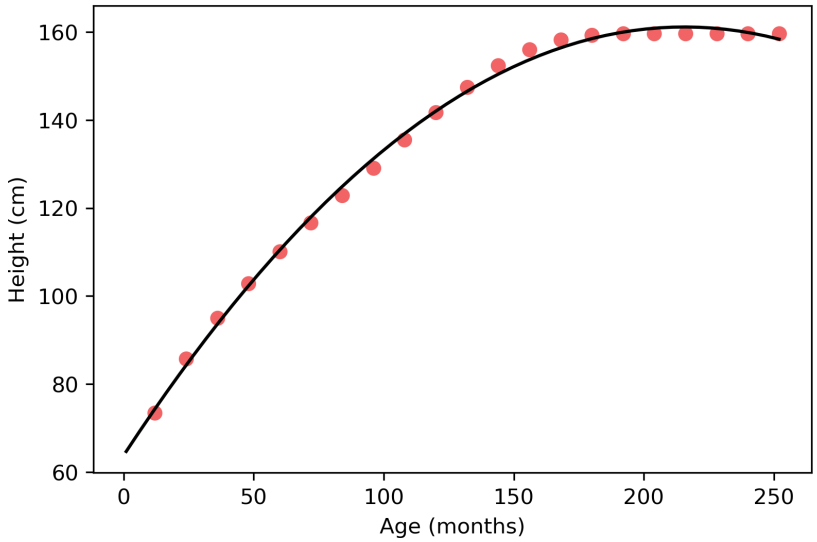

Figure C.4: Function for growth formula for women with Hindustan ethnicity. The pink markers are the data points and the black line is the fitted equation: $-0.002095 \times x^2 + 0.9032x + 63.77$ where x is the age in month. Note that we have used the growth chart for Surinamese women as a proxy for Hindustan women

C.2. Population growth

In section 4.4.11 we present the equation for the expected population growth. Here, we present Figure C.5 that illustrates the total population growth. The pink markers are the data points from the dataset from Centraal Bureau voor de Statistiek (2019b). The black line illustrates Equation 4.13.

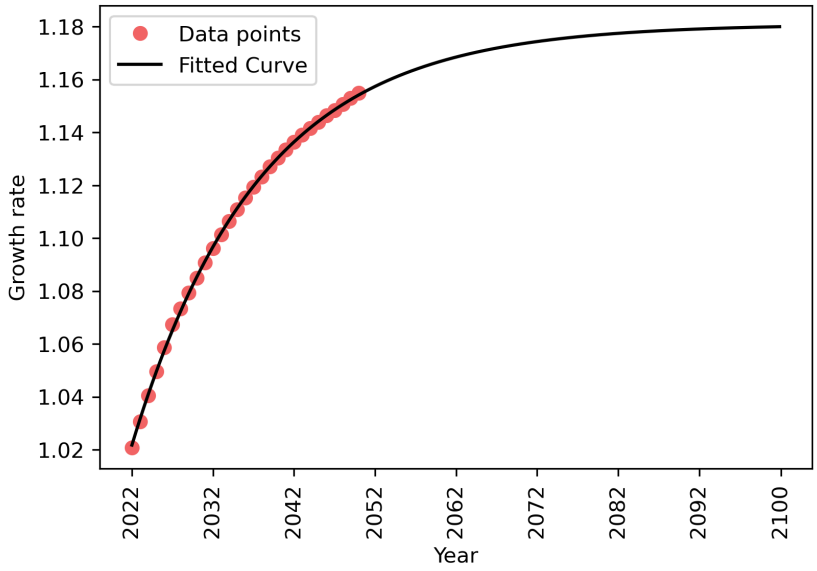

Figure C.5: Predicted growth rate of the Hague.

C.3. Population growth per ethnicity

Centraal Bureau voor de Statistiek has made several predictions about the composition of the population of the Hague. It is expected immigration will be the main driver for the increase. This has multiple effects. Firstly, this decreases the number of available resources per citizen, and secondly, this affects social networks. The projected growth per ethnicity are shown in Figures C.6, C.7, C.8 and C.9 for the Dutch, Turkish, Moroccan and Surinamese population respectively. The red markers are the data points, the black line is the fitted line, and the horizontal grey line shows were 0 is. The pink line is an assumption made by us: at this point, we assume the population will not increase or decrease. The X–axis shows the fraction of decrease or increase. In other words: it is projected the Dutch and Suriname will proportionally decrease in size, whereas the Moroccan and Turkish ethnicities will proportionally increase in size.

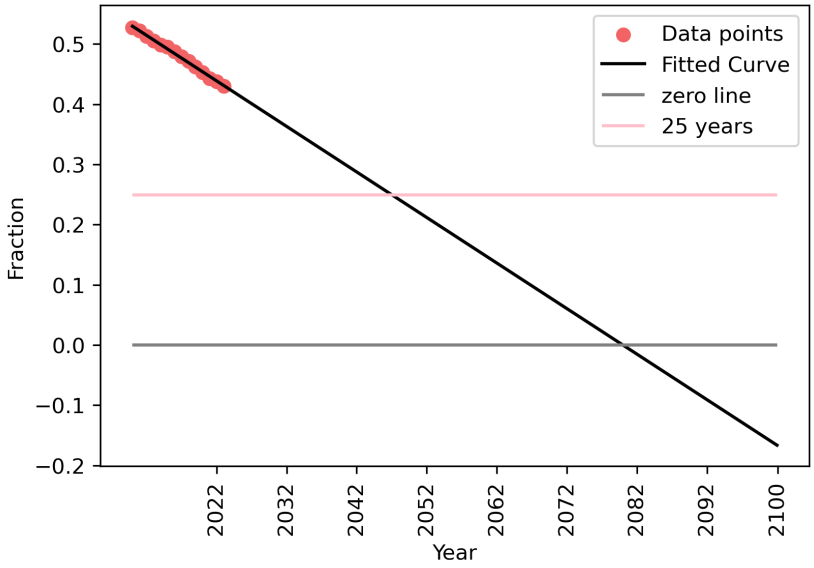

Figure C.6: Predicted fraction of the population of the Hague that will be Dutch. The corresponding fitted equation is $-0.0006304 \times x + 0.4388$.

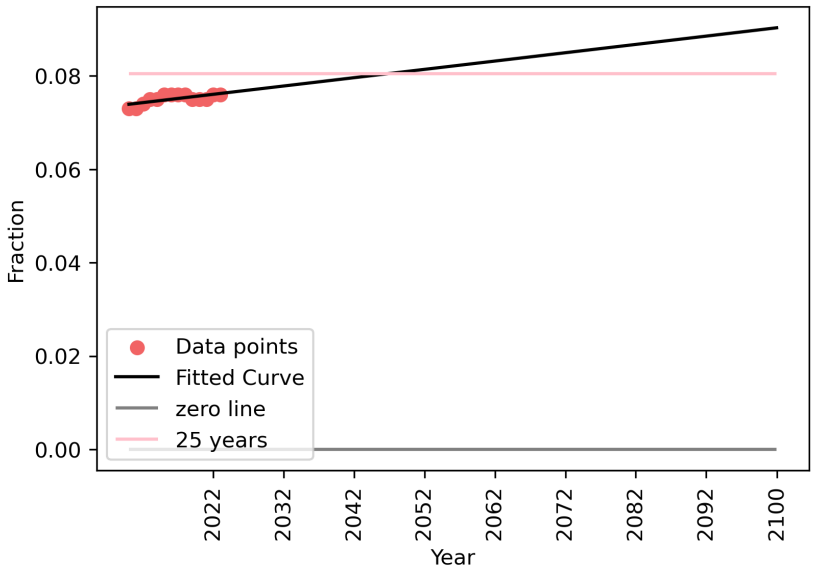

Figure C.7: Predicted fraction of the population of the Hague that will be Turkish. The corresponding fitted equation is $1.484e-05 \times x + 0.07605$.

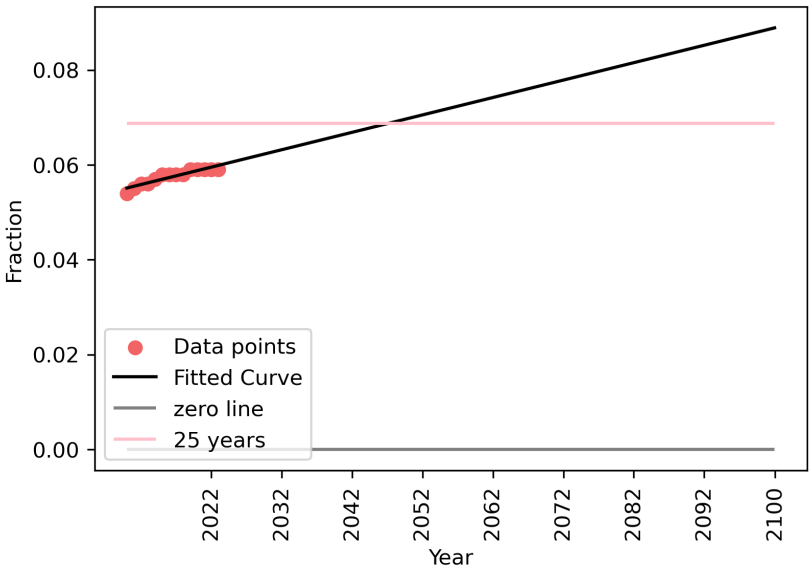

Figure C.8: Predicted fraction of the population of the Hague that will be Morrocan. The corresponding fitted equation is $3.059e-05 \times x + 0.05952$.

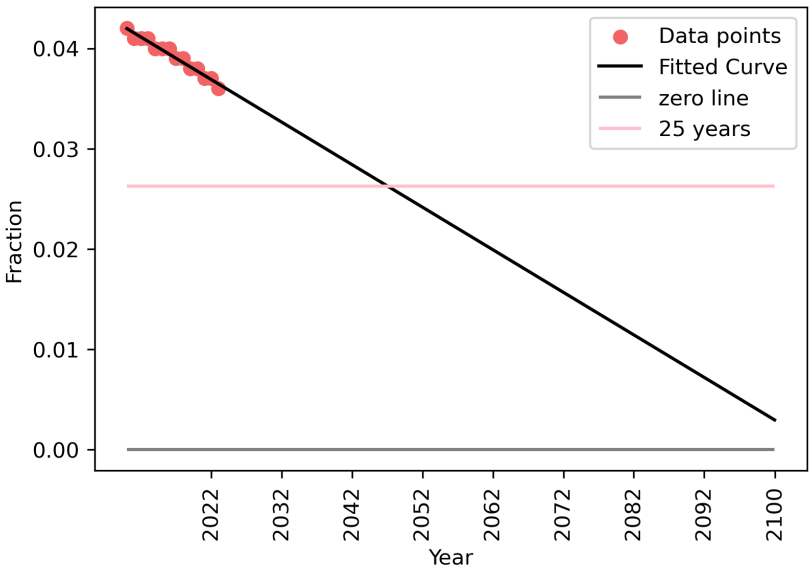

Figure C.9: Predicted fraction of the population of the Hague that will be Surinamese. The corresponding fitted equation is $-3.535e-05 \times x + 0.03688$.

C.4. Number of friends

The friend module keeps track of the number of friends each woman has based on her age. To get the values we use the dataset provided by K. Bhattacharya et al. (2016). In Figure C.10 we display all data points as blue markers, and the continuous line fitted to the data in red. The fitted line has the formula shown in Equation C.1 where x is the age of the woman in years. The model makes use of the mean and standard deviation for the cuts shown in Table C.1.

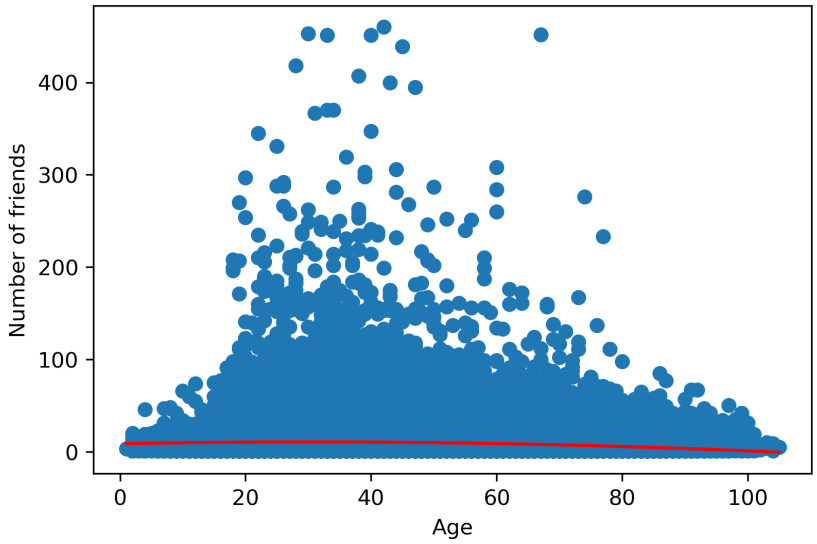

Figure C.10: Number of friends.

$$-0.002012 \times x^2 + 0.1225 \times x + 8.681 \tag{C.1}$$

Table C.1: The mean and standard deviation of the number of female friends.

Age group	Mean	SD
(12, 16]	5.01	4.04
(16, 20]	8.01	9.37
(20, 26]	10.82	9.87
(26, 31]	11.39	9.57
(31, 36]	11.13	9.09
(36, 46]	10.01	8.62
(46, 51]	9.36	8.08
(51, 56]	9.17	7.70
(56, 70)	8.28	6.94
(70, 80]	6.76	5.86
(80, 110]	6.14	5.38

C.5. Ethnicity distribution in social circles

Figure C.11 shows the number of women that were included in the NELLS dataset (Tolsma et al., 2014). Figure C.12, C.13, C.14 show that the compositions of the social circles of Moroccan, Turkish and Dutch women is not really affected by age.

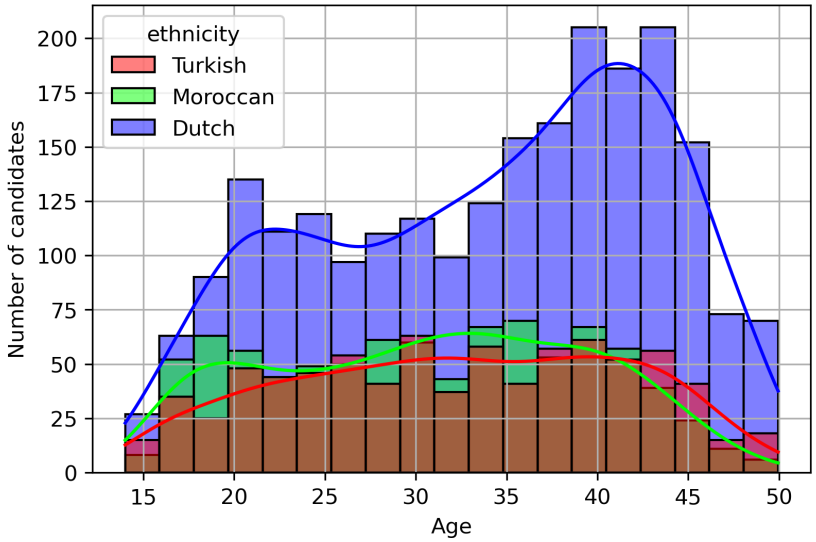

Figure C.11: Amount of female candidates in the NELLS study. Shown per ethnicity and age.

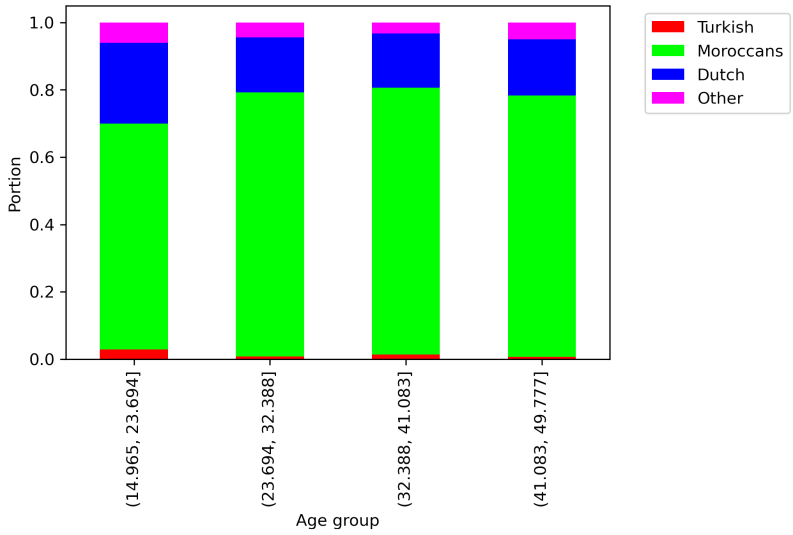

Figure C.12: The compositions of the social circles of an average Moroccan woman over age.

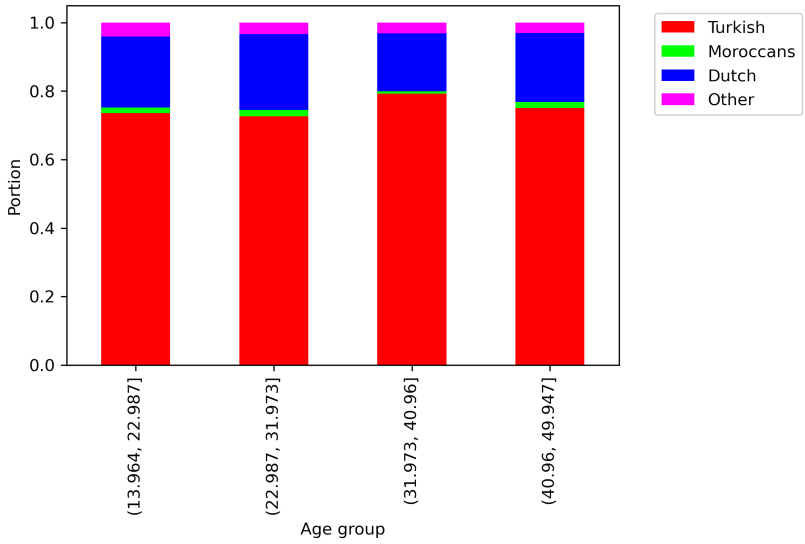

Figure C.13: The compositions of the social circles of an average Turkish woman over age.

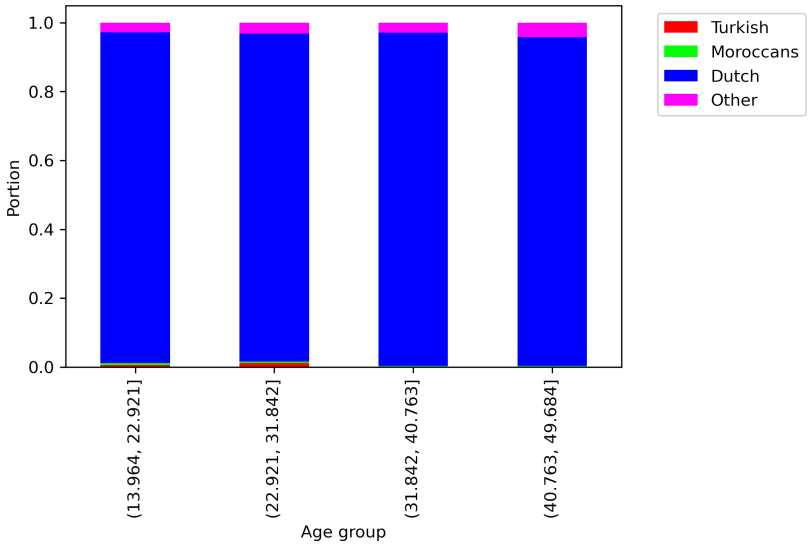

Figure C.14: The compositions of the social circles of an average Dutch woman over age.

C.6. Fine and Gray Model to calculate the 10-year risk of a first-ever mace

A fine and gray model (FGL model) was developed to calculate the 10-year risk of a first-ever mace for women in the Hague. It was trained on the private Extramuraal LUMC Academisch Netwerk (ELAN) dataset, and to be specific only on the women (Leiden University Medical Center, n.d.). Data from and Centraal Bureau Statistiek (CBS) was used to augment the health data with personal data.

The ELAN dataset included a lot of missing values, as can be seen in Table C.2. Initially, we were interested in training the Fine and Gray model on variables including BMI. However, the training set would be too small, due to the large number of records that missed the BMI variable. Because of the high number of missing values, it was bad practice to apply a imputation technique, such as the multivariate imputation by chained equations algorithm, to guess possible BMI values (Jakobsen et al., 2017). To increase the reliability of the Fine and Gray model we thus decided to leave out BMI as an independent variable.

Table C.2: Percentage of missing values per variable in the available dataset.

Variable	**Percentage**
Systolic blood pressure	50.76
Fasting blood glucose	52.27
Non-fasting blood glucose	72.94
Total Cholesterol	61.66
HDL Cholesterol	63.62
Cholesterol HDL ratio	65.03
BMI	77.94

The number of events per age group is shown in Figure C.15. As to be expected, most maces in the records are in the older age groups. Interestingly, a lot of MACEs occurred before the age of 60. This strengthens our claim that the current manual may be out-of-date, as it claims only women over the age of 60 are at a very high risk of getting a MACE (Nederlands Huisartsen Genootschap, 2019) .

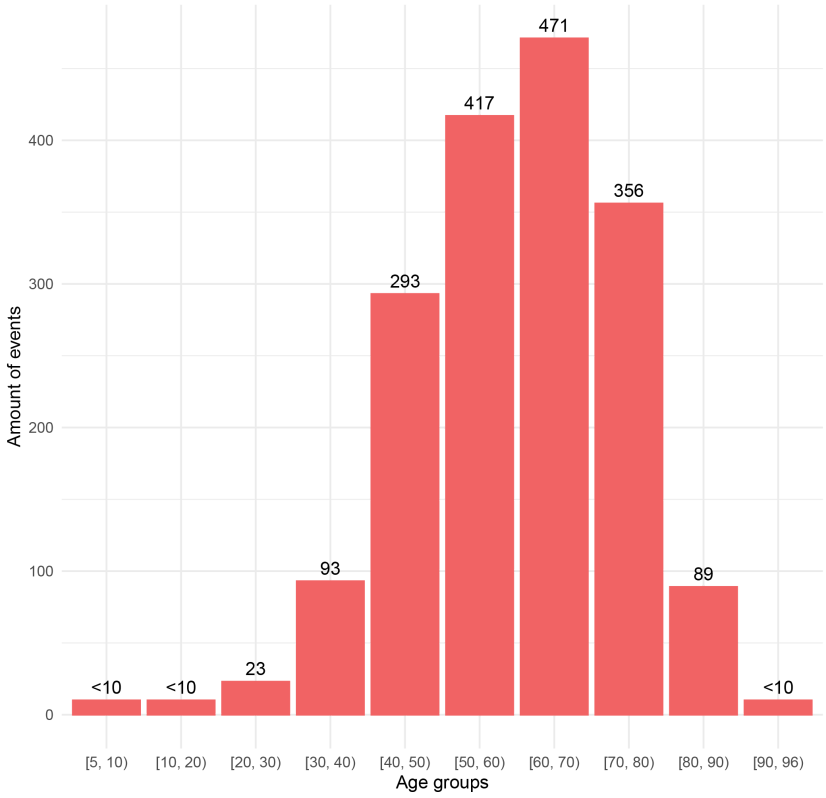

Figure C.15: The number of maces in the dataset the Fine and Gray model was trained on per age group.

We did find that we had too little data to include ethnicity as a factor, as there were simply not enough MACEs per ethnicity. We were able to increase the number of usable records in the dataset by interpolating the fasting glucose, blood pressure and total cholesterol values.

The Fine and Gray model was trained on the following variables: age (continuous), fasting glucose (continuous), systolic blood pressure (continuous), total cholesterol (continuous), use of statins (binary), use of antihypertensions (binary), medication for diabetes (binary), is smoking (binary), has smoked in the past (binary), income (categorical). Table C.3 shows the summary statistics for the independent variables used in the Fine and Gray model. The Fine and Gray model was trained on 29936 records. Note that there is some skewness in the training set. For the Fine and Gray model we used the same cuts for income as used in the simulation model.

Table C.3: A categorical variable consists out of multiple levels and has *(cat)* preceding its name. In that case, the count and percentage are given. If a variable was continuous, the table shows the mean and standard deviation.

Type	**Name**	**Level**	**Mean/Count**	**Standard Deviation/Percentage**
Demographics	Age		50.34	15.28
	(cat) Income	0	19700	65.8
	(cat) Income	1	8982	30.0
	(cat) Income	2	1254	4.2
Medical	Total blood cholesterol		5.44	1.16
	Fasting blood glucose		5.73	1.63
	Systolic blood pressure		135.28	22.44
Medication	(cat) Diabetes	0	24382	81.4
	(cat) Diabetes	1	5554	18.6
	(cat) Hypertension	0	29604	98.9
	(cat) Hypertension	1	332	1.1
	(cat) Dyslipidemia	0	25758	86.0
	(cat) Dyslipidemia	1	4178	14.0

Health behaviours	(cat) Current smoker	0	19861	66.3
	(cat) Current smoker	1	10075	33.7
	(cat) Past smoker	0	26213	87.6
	(cat) Past smoker	1	3723	12.4

We opted for this combination of variables, and to be precise, the formula shown in Equation C.2, as it performed best. Different formulas were tried ad hoc. The performance of this formula can be seen in Figures C.16, C.17 and C.18. The first two figures are used to assessed the discriminative power of the model, whereas the latter shows how well the model is calibrated. The first figure shows the area under the curve over time (the AUC), which shows the discriminative abilities of the Fine and Gray model. We can see it is just slightly below 0.8, meaning the discriminative accuracy is very close to good (Zhang et al., 2018). In the first months, the model scores above 0.8, after which the performance decreases, possibly due to a lack of training data, and then its discriminative power somewhat stabilises. The second figure shows the Brier score over time. The Brier score is the expected distance between the observed status at that time and the predicted probability. Thus, the smaller the Brier score, the better the model performs (Zhang et al., 2018). We can see that the Brier score increases over time. This indicates that there may be other variables, not present in the dataset, that could increase the performance of the model. This is also supported by the fact that the Fine and Gray model only slightly outperforms the null model. The final figure displays the calibration curve, which compares actual risk against predicted risk. Thus, the closer the curve to the diagonal, the better the model. We see it starts deviating from the diagonal at about 14%, which suggests there will be an underestimation in the higher risk group.

We would like to emphasise that, during the data analyses for the Fine and Gray, we confirmed the observation made by Zhao et al. (2016): a low total cholesterol is associated with a higher MACE risk. Our finding, thus also, clashes with several studies that found an association between high total cholesterol levels and a reduced CVD risk (Cui et al., 2012; von Büdingen et al., 2008). The association between blood pressure and fasting blood glucose with CVD risk is, however, positive, which is also supported by many studies (Khan et al., 2014; Kokubo, 2012; Prabhakaran & Chong, 2014).

$$\texttt{age} + (1 + \texttt{age}) \times (\texttt{systolic blood pressure} + \texttt{fasting glucose value} + \texttt{total cholesterol value} + \\ + \texttt{former smoker} + \texttt{diabetes medication} + \texttt{hypertension medication} + \texttt{cholesterol medi} \tag{C.2}$$

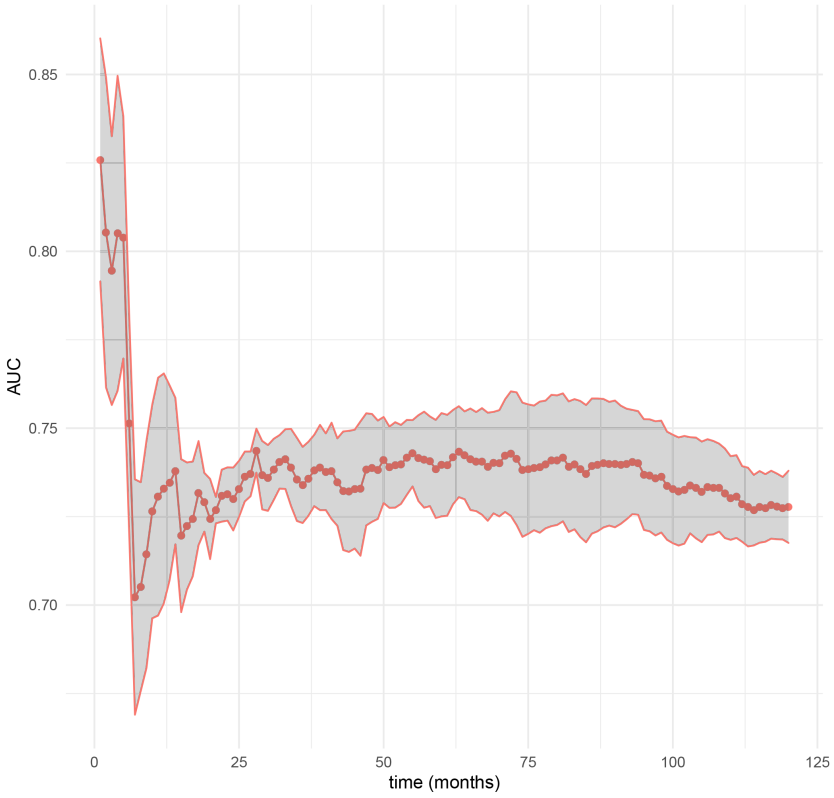

Figure C.16: The area under the curve over time of the Fine and Gray model.

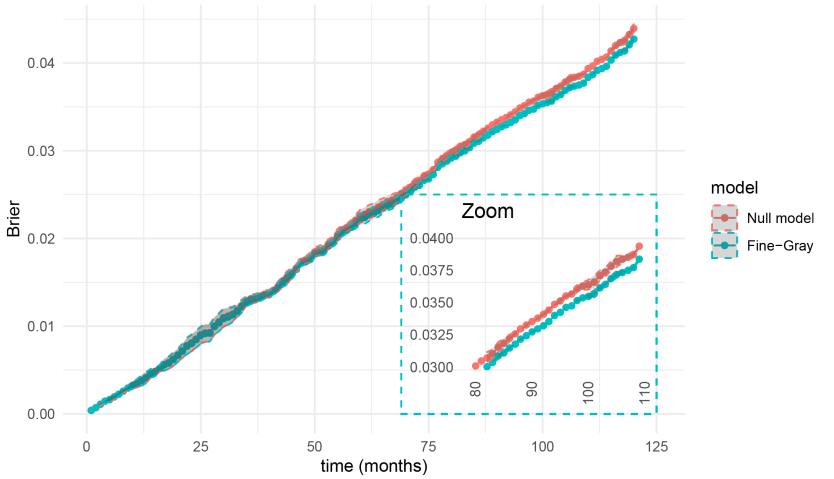

Figure C.17: The Brier score over time of the Fine and Gray model.

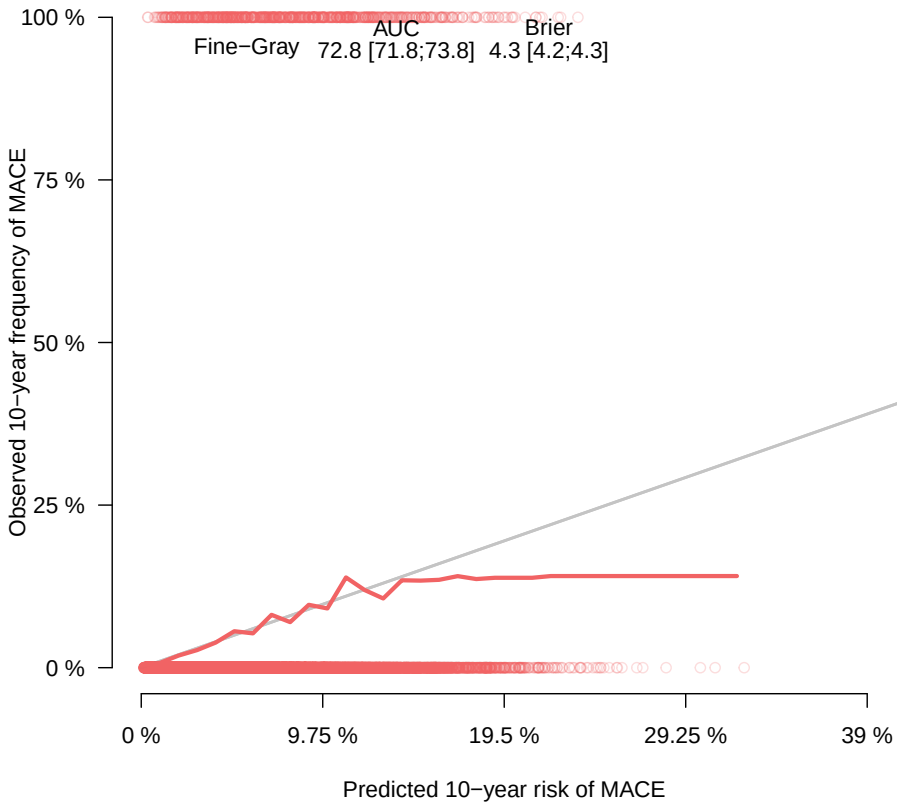

Figure C.18: The calibration curve of the Fine and Gray model. The graph also shows the AUC score and the Brier score of the step of interest, the 10 year point.

The total formula, including the coefficients are shown in Table C.4. The sensitivity analysis of the model is described in Chapter 6.

Table C.4: The variables of the Fine and Gray model and their coefficients

variables	**coefficient**
age	0.088910489
systolic blood pressure	0.014041348
fasting glucose value	0.066393792
total cholesterol value	−0.01437952
(1 if smoker)	1.357162143
(1 if former smoker)	0.50814904
(1 if diabetes medication)	0.612456747
(1 if hypertension medication)	1.150785479
(1 if cholesterol medication)	1.436480851
(1 if income < 31700)	−0.257561431
(1 if income ≥ 31700 and income ≤ 62700	−0.240799376
age × systolic blood pressure	−0.000171793
age × fasting glucose value	−0.000893179
age × total cholesterol value	−0.000870519
age × (1 if smoker)	−0.014488459
age × (1 if former smoker)	−0.003063906

age × (1 if diabetes medication)	-0.004455506
age × (1 if hypertension medication)	-0.0128246
age × (1 if cholesterol medication)	-0.018156462

C.7. GLMs for fasting blood glucose, total cholesterol and blood pressure

Since the GLM depends on fasting blood glucose, total cholesterol and blood pressure values, we needed to include a mechanism for the agents to generate these values. for this purpose, we trained three generalised linear models (GLMs). For systolic blood pressure, we used the inverse gaussian distribution, and for the other two a gamma distribution. All GLMs are trained on age, BMI, ethnicity and medication.

It is known there is a strong correlation between age and BMI and the dependent variables: blood glucose levels, cholesterol levels and blood pressure (Fikriana & Devy, 2018; Mokdad et al., 2003). Hence why age and BMI are the independent variables. We also included ethnicity, as this has also been shown to impact all three dependent variables (Agyemang et al., 2007; Ujcic-Voortman et al., 2010; van Vliet et al., 2009). Since we are actually looking at the Hague, there are two possible hypotheses why including ethnicity improves the performances of the GLMS. First, in past years it seems the population of the Hague has only become more segregated (Meijers et al., 2014). It has even been called the most segregated city in the Netherlands (Kloosterman & Priemus, 2001). This means that the ethnicity variable represents the neighbourhood environment up to a certain extent. Secondly, they may be more susceptible due to genetic predisposition shared by the cohort.

The units of fasting blood glucose and blood cholesterol are mmol/L, whereas systolic blood pressure has the unit mmHg. Note that we do not know which fasting blood glucose levels belonged to people with Type 1 or to people with Type 2 diabetes. We assumed there were substantially more people with Type 2 diabetes in the dataset, hence why this was deemed acceptable.

Eventually, we combined the ELAN dataset with the microdata datasets from CBS to include records on the date of birth, date of the first MACE, age, ethnicity, fasting blood glucose level, total cholesterol level, BMI, systolic blood pressure, whether the subject is smoking, whether the subject has smoked, income (based on standardised household income) and three types of medication use. All models were only trained on women in Leiden and the Hague. Some interpolation was performed to fill in missing values. The baseline characteristics of the populations are shown in Table C.5.

Table C.5: Summary statistics of independent variables used to train the GLMs

Name	**level**	**Dutch**	**Turkish**	**Moroccan**	**Surinamese**	**Other**
Fasting blood glucose						
Number of records		70857	6003	5690	17510	31268
Age		65.42 (14.81)	48.71 (15.23)	49.91 (14.65)	54.13 (13.36)	57.09 (15.28)
BMI		28.82 (5.92)	32.84 (6.32)	31.78 (5.61)	28.91 (5.49)	29.77 (6.35)
(cat) Medication	0	39027 (55.1)	2912 (48.5)	1857 (32.6)	6145 (35.1)	15889 (50.8)
(cat) Medication	1	31830 (44.9)	3091 (51.5)	3833 (67.4)	11365 (64.9)	15379 (49.2)
Total cholesterol		6.53 (1.96)	6.62 (2.36)	7.08 (2.15)	6.82 (2.11)	6.61 (2.24)
Total cholesterol						
Number of records		69051	5211	4994	16251	29226
Age		65.71 (14.25)	50.41 (14.09)	51.58 (13.50)	54.91 (12.71)	58.05 (14.42)
BMI		28.80 (5.86)	33.22 (6.22)	31.98 (5.49)	28.94 (5.45)	29.77 (6.27)
(cat) Medication	0	33227 (48.1)	2689 (51.6)	2468 (49.4)	7226 (44.5)	15544 (53.2)
(cat) Medication	1	35824 (51.9)	2522 (48.4)	2526 (50.6)	9025 (55.5)	13682 (46.8)
Total cholesterol		5.20 (1.18)	5.03 (1.11)	4.58 (1.00)	4.85 (1.08)	5.07 (1.15)
Systolic blood pressure						
Number of records		85574	6215	6069	18649	35165
Age		64.51 (16.08)	48.65 (15.18)	49.03 (15.09)	53.77 (13.68)	56.72 (15.70)
BMI		28.47 (5.91)	32.40 (6.50)	31.45 (5.77)	28.76 (5.49)	29.50 (6.36)
(cat) Medication	0	83692 (97.8)	6118 (98.4)	5980 (98.5)	18276 (98.0)	34160 (97.1)

(cat) Medication	1	1882 (2.2)	97 (1.6)	89 (1.5)	373 (2.0)	1005 (2.9)
Systolic blood pressure		138.68 (20.11)	129.79 (19.59)	129.64 (19.54)	132.79 (19.13)	135.16 (19.75)

The performance of the GLMs is shown in Table C.6. The AIC and BIC are the Akaike information criterion and Bayesion information criterion respectively. They are two statistical approaches to estimate the fitness of the models to the dataset. The lower the scores, the better the performance. R^2 measures the goodness of fit of a model, as it represents the proportion of variance in the dependent variable, either being total cholesterol, systolic blood pressure or fasting blood glucose that is predictable from the independent variables. The R^2 values are low, meaning that unfortunately, the models do not properly explain the variability of the response data around the mean. The Root Means Square Error (RMSE) is the square root of the average squared errors. It is also a way to measure the fitness of the model. We can see the RMSE for the systolic blood pressures is quite high. Note that this is also because the values of blood pressures are in general higher, meaning that the difference would have been less if the values were normalised. All RMSE values are quite high, indicating there may be a better combination of variables we did not have access to, would produce a better model. Finally, the family is shown that was used to generate the models. We implemented the Inverse Gaussian model of the systolic blood pressure GLM, but wanted to show the performance of the same model, using the Gamma distribution.

Table C.6: Summary statistics of independent variables used to train the GLMs

model	**observations**	**AIC**	**BIC**	R^2	**RMSE**	**Family**
total cholesterol	124733	371077.25	371164.86	0.11	1.19	Gamma
systolic blood pressure	151672	1308758.50	1308847.87	0.15	18.62	Inverse Gaussian
fasting blood glucose	131328	453954.99	454043.06	0.40	1.76	Gamma
systolic blood pressure	151672	1310590.26	1310679.62	0.15	18.65	Gamma

Table C.7: The variables and their coefficients for the systolic blood pressure GLM

variables	**coefficient**
intercept	4.615486142
age	0.003281668
BMI	0.003622011
(1 if ethnicity = Moroccan)	-0.029742074
(1 if ethnicity = Other)	-0.004689994
(1 if ethnicity = Surinamese)	-0.00986527
(1 if ethnicity = Turkish)	-0.030409928
(1 if hypertension medication)	0.042259339

Table C.8: The variables and their coefficients for the total fasting blood glucose GLM

variables	**coefficient**
intercept	0.206160442
age	$-9.97346E-05$
BMI	-0.000672402
(1 if ethnicity = Moroccan)	-0.000978433
(1 if ethnicity = Other)	$3.66065E-05$
(1 if ethnicity = Surinamese)	0.001683327
(1 if ethnicity = Turkish)	0.002222404
(1 if diabetes medication)	-0.050209203

Table C.9: The variables and their coefficients for the systolic blood pressure GLM

variables	**coefficient**
intercept	4.615486142
age	0.003281668
BMI	0.003622011
(1 if ethnicity = Moroccan)	−0.029742074
(1 if ethnicity = Other)	−0.004689994
(1 if ethnicity = Surinamese)	−0.00986527
(1 if ethnicity = Turkish)	−0.030409928
(1 if hypertension medication)	0.042259339

Multiple formulas were tested. But these formulas were the most promising ones.

Finally, more information about the residuals can be found in Figures C.19 to C.24. Each pair of plots is about the residuals of the GLM for total cholesterol, fasting blood sugar and systolic blood pressure respectively. The Q-Q plots for all models show that the data normality assumption to perform linear regression: The data is compared to a normal distribution and are plotted against each other. All Q-Q plots are straight lines, except for their tails. The Q-Q plot for cholesterol shows the data is somewhat skewed to the right. The Q-Q plots for the fasting glucose value GLM and the systolic blood pressure GLM shows there are more datapoints at the extremes of the distribution than in the center. The Residuals vs Fitted plots are scatter plots of residuals versus the estimations of the models. In all plots we can see that the residuals are are distributed randomly in a horizontal band around the residual line. We do however see some outliers. The resiudals vs fitted plot of the fasting glucose plot shows two clusters, however, this only indicates that the original dataset contained these clusters.

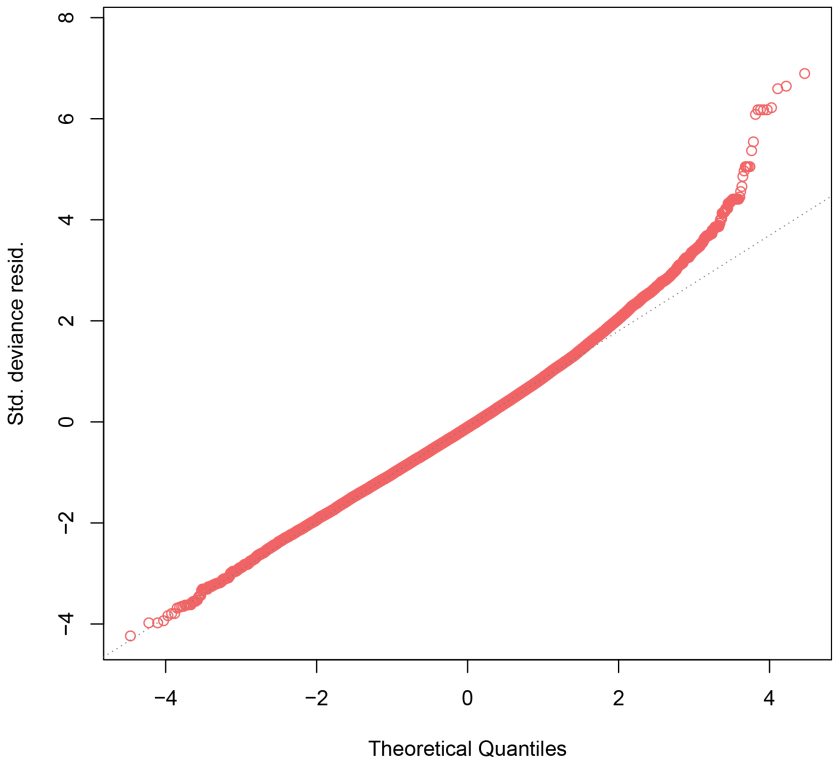

Figure C.19: The Q-Q plot of the total cholesterol GLM.

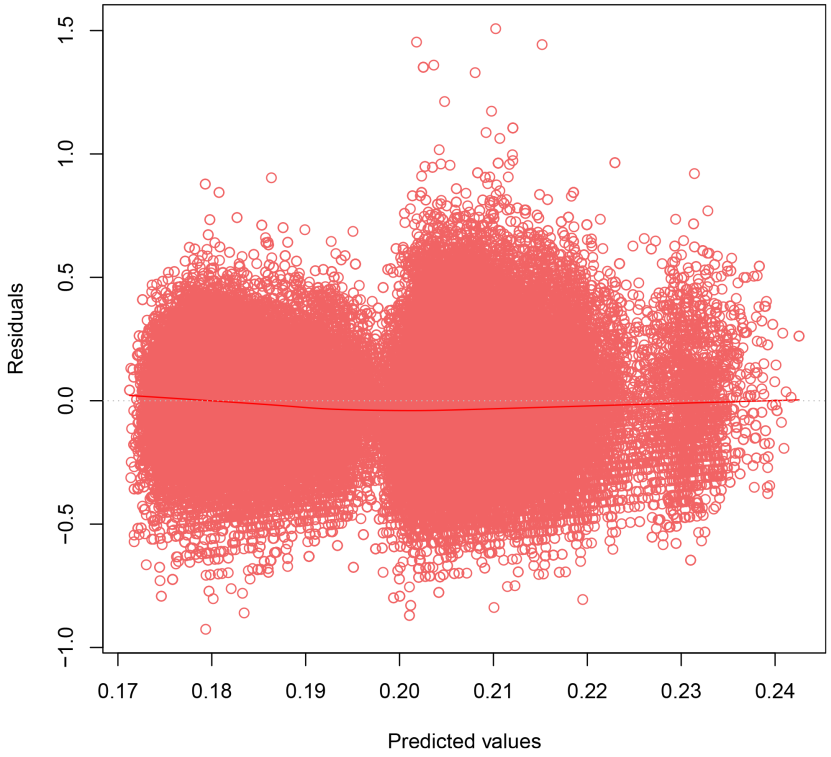

Figure C.20: The residuals vs fitted plot of the total cholesterol GLM.

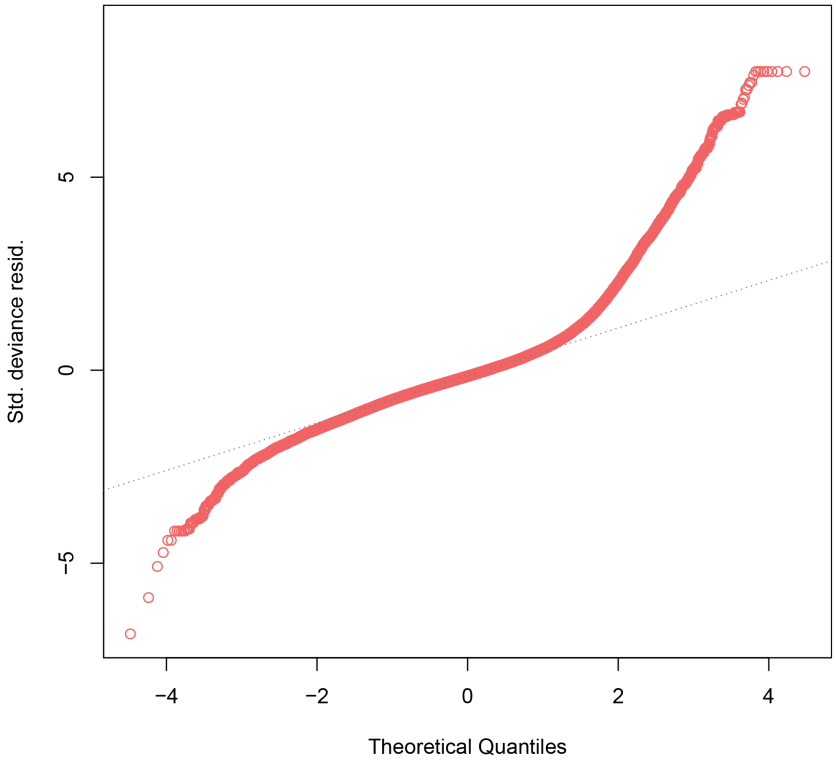

Figure C.21: The Q-Q plot of the fasting blood glucose GLM.

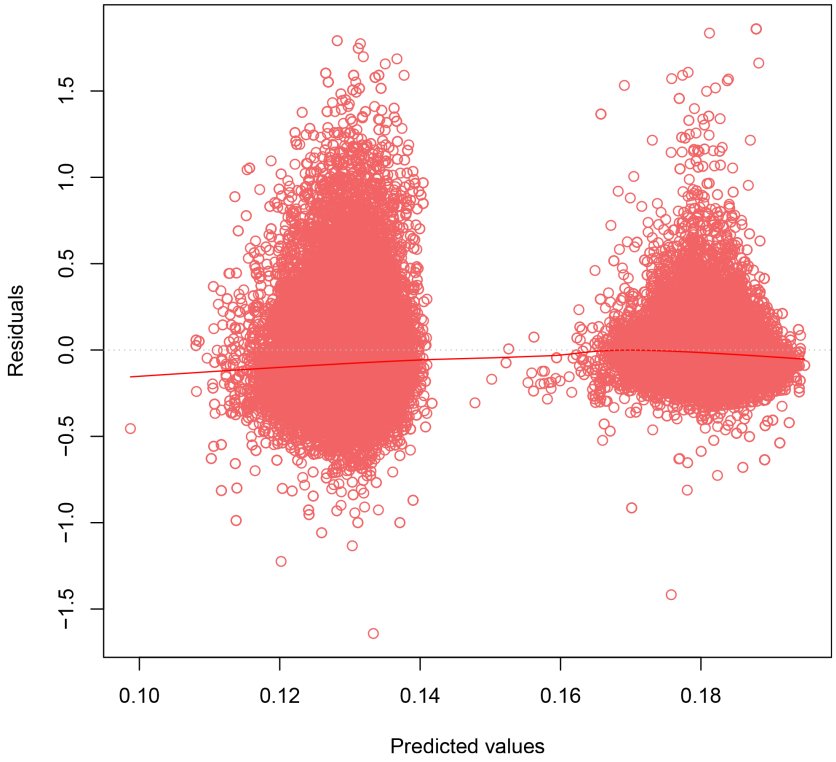

Figure C.22: The residuals vs fitted plot of the fasting blood glucose GLM.

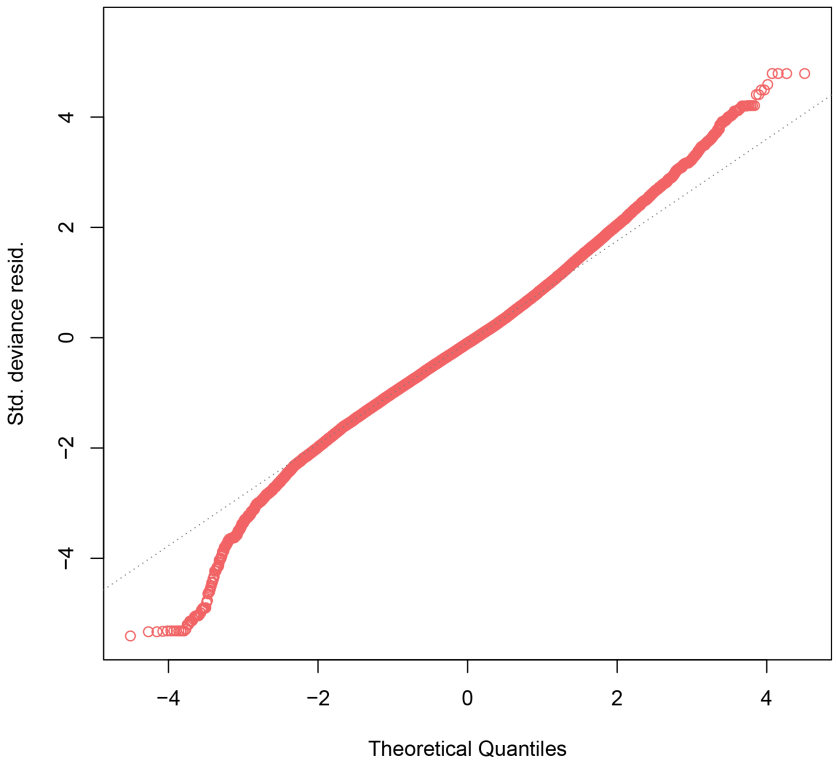

Figure C.23: The Q-Q plot of the systolic blood pressure GLM.

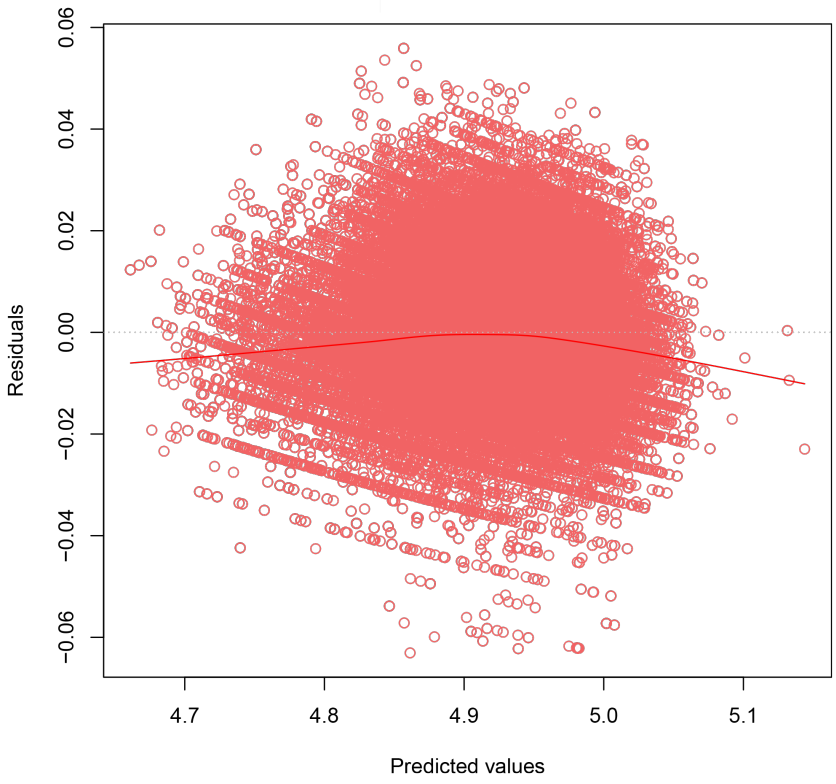

Figure C.24: The residuals vs fitted plot of the fasting blood glucose GLM.

C.8. Income distributions over ethnicity

Data from CBS on women in the Hague was used to calculate the income distributions among the several ethnicities used in the model. The results are shown in Table C.10.

Table C.10: Distribution of income per ethnicity. 26497 observations were used, of women only, to calculate the values below. The cut-off points are the ones used by Den Haag in Cijfers et al. (2021), and are as such: 0: < 31700, 1: $>= 31700$, 2: $>= 69701$

Level	Percentage
Dutch	
0	54.8
1	38.6
2	6.6
Turkish	
0	76.1
1	21.0
2	2.9
Moroccan	
0	86.7
1	12.0
2	1.3
Surinamese	
0	65.2
1	32.5
2	2.3
Other	
0	64.6

1	23.8
2	11.6

D

More detailed look at the interventions Targeted, Smoking and School

In this chapter we take a closer look at the effects of the interventions *Targeted*, *Smoking* and *School*. We both compare the effects between the interventions, but also look at the different versions of each intervention. We start by looking at the effects per scenario. Finally, we show the effects of the best performing interventions per scenario side by side for each scenario.

D.1. The effects of the three interventions on each scenario

In this section we dissect the effects of the three interventions on each scenario, starting with scenario 1. Compared to scenario 1, women in scenario 2 are more likely to start smoking and less likely to stop smoking. In scenario 3, women are more susceptible to influence from their social network.

D.1.1. Scenario 1

Figure D.1 shows the number of average MACE events per cut. Based on the overview of the graphs only one intervention shows real promise, namely *School 4*. On the whole, the difference between all interventions and the baseline is rather small as shown by the small range of the x-axes.

The first cut equals the first seven years of the simulation. We see that all variations outperform the base case represented in the blue line, but for version 3 of the *Targeted* intervention. This is interesting as this intervention has the same frequency as version 5. Version 3 affects only 200 women, whereas version 5 affects 400. Version 2 also affects the same number of women as version 3, but has a frequency of 4 years opposed to 1 year. Version 1 is the best performing variation, but its performance is equal, if not worse, than the base case. This is interesting as it is the intervention that affects the least number of people and also the intervention with the lowest frequency (of 4 years).

All variations of the *Smoking* intervention are successful in the first two cuts. Then we see the number of MACE events increasing for each variation. It may be the case that the difference between the number of MACE events between each variation and baseline is simply due to old age. Due to the intervention, more women are getting older, making them more likely to get a MACE event due to a risk factor they have no control over. Initially, the third variation seems most promising. This variation is the least invasive of the four.

The *School* intervention is promising as there is some indication its effects may be long-lasting. In scenario 1, the variation that is repeated every 6 years for just one month, and that only reaches 30% of the children outperforms all other variations. The other variations have a bigger reach and duration, but a smaller frequency. This indicates that frequency, and thus, repeatedly affecting health behaviours, makes more impact than the duration of the intervention and the amount of girls that are being reached.

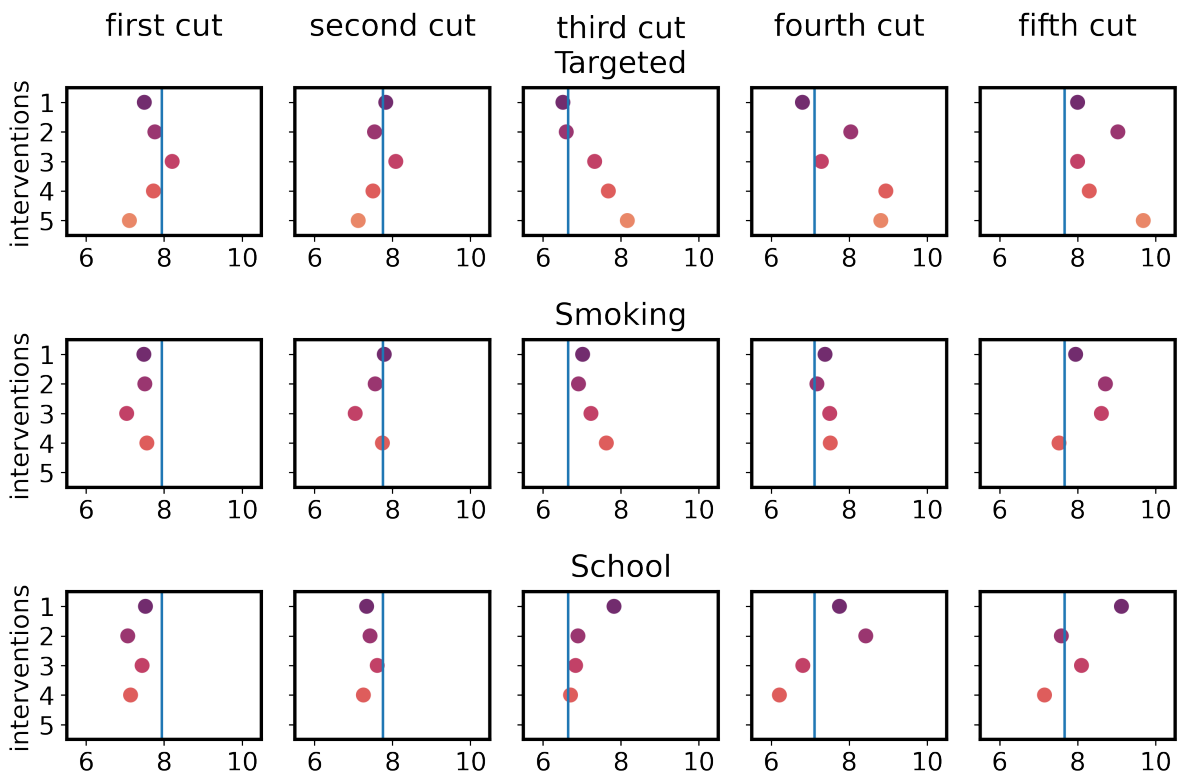

Figure D.1: The average number of MACE events when the interventions are in place in scenario 1. The first cut equals the first seven years years, the second cut the second ten years, and so on. The blue lines represent the values of the base case.

Figure D.2 shows the average age of women getting a MACE. It clearly shows the population is ageing, as every cut, the average age increases. The only intervention that stands out when observing the graphs is *Targeted 4*, which is the most intensive *Targeted* intervention: it negatively affects this KPI. All other interventions perform similarly to the baseline.

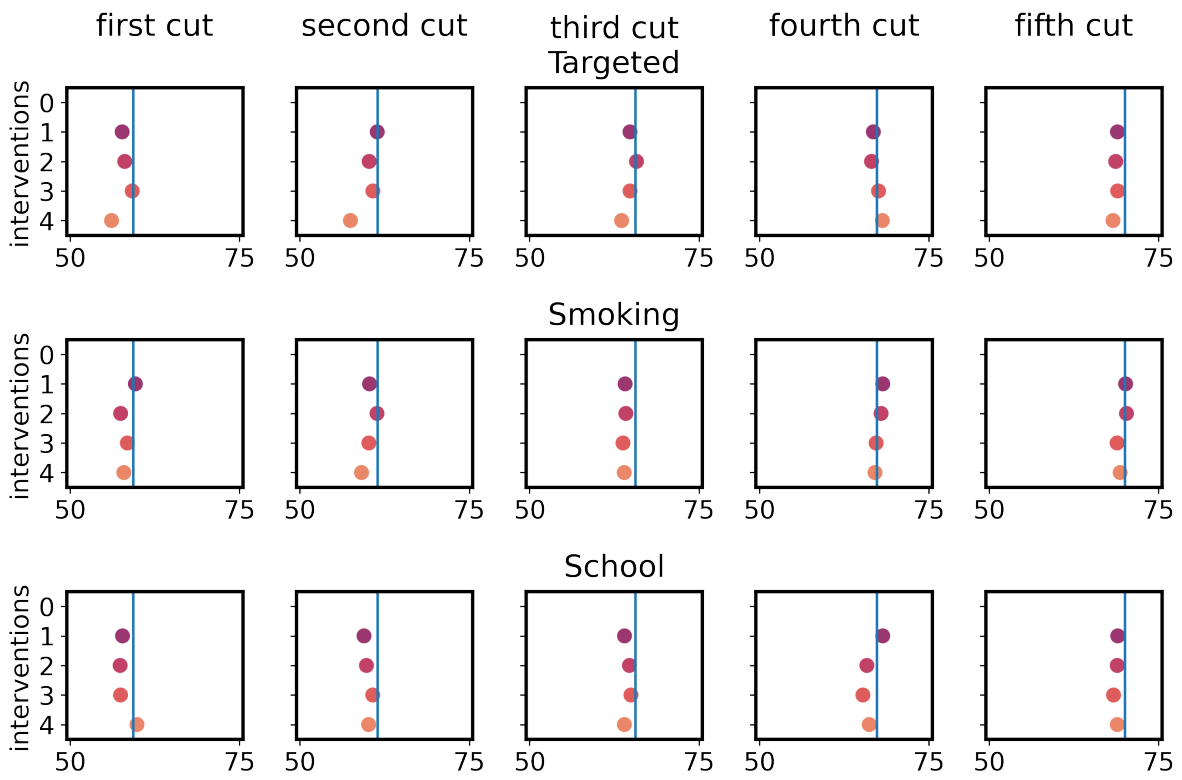

Figure D.2: The average age of women getting a MACE events when the interventions are in place in scenario 2. The first cut equals the first seven years years, the second cut the second ten years, and so on. The blue lines represent the values of the base case.

D.1.2. Scenario 2

Scenario 2 is the scenario where women are more likely to start and less likely to stop smoking. The impact of the scenarios on the average number of MACE events per cut are shown in Figure D.3. As with scenario 1, *School 4* appears to be a promising intervention as it either does not seem to affect the base case or improves the KPI.

Regarding the *Targeted* interventions, the first variation, which is the least intensive one, outperforms all other variations. The second variation is at a close second. It seems that the more intensive the intervention is, the less positively it can affect the outcome for the female population in the Hague.

For the *Smoking* intervention, there is no variation that greatly improves the outcome. The second and third variations outperform the others. Just as with the *Targeted* interventions, these are the least intensive variations.

The graphs show that the *School* intervention is the least effective intervention of all three. The first variation performs slightly better than the other variations.

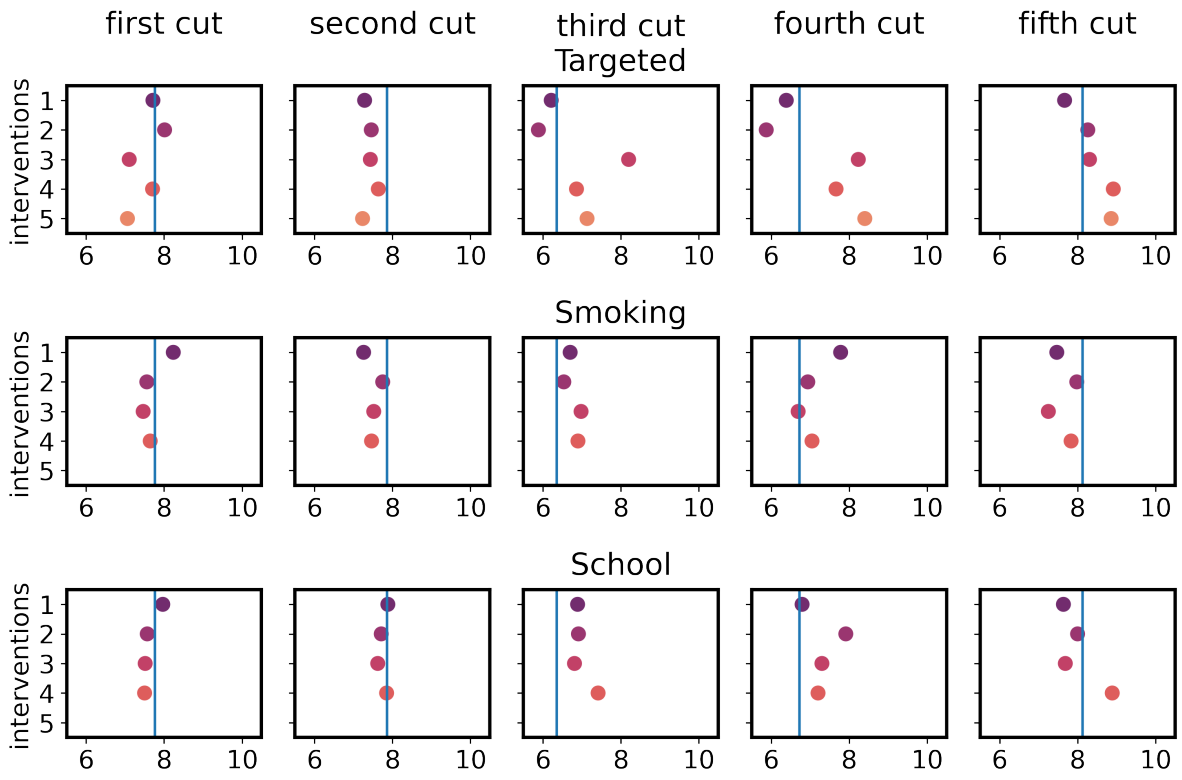

Figure D.3: The average number of MACE events when the interventions are in place in scenario 2. The first cut equals the first seven years years, the second cut the second ten years, and so on. The blue lines represent the values of the base case.

The graphs in Figure D.4 show the average age that women getting a MACE event have in scenario 2. *Targeted* interventions variations 2, 3 and 4, negatively impact this outcome in the first two cuts. Most interventions seem to either not affect the value from the base case, or slightly improve it in the last two cuts.

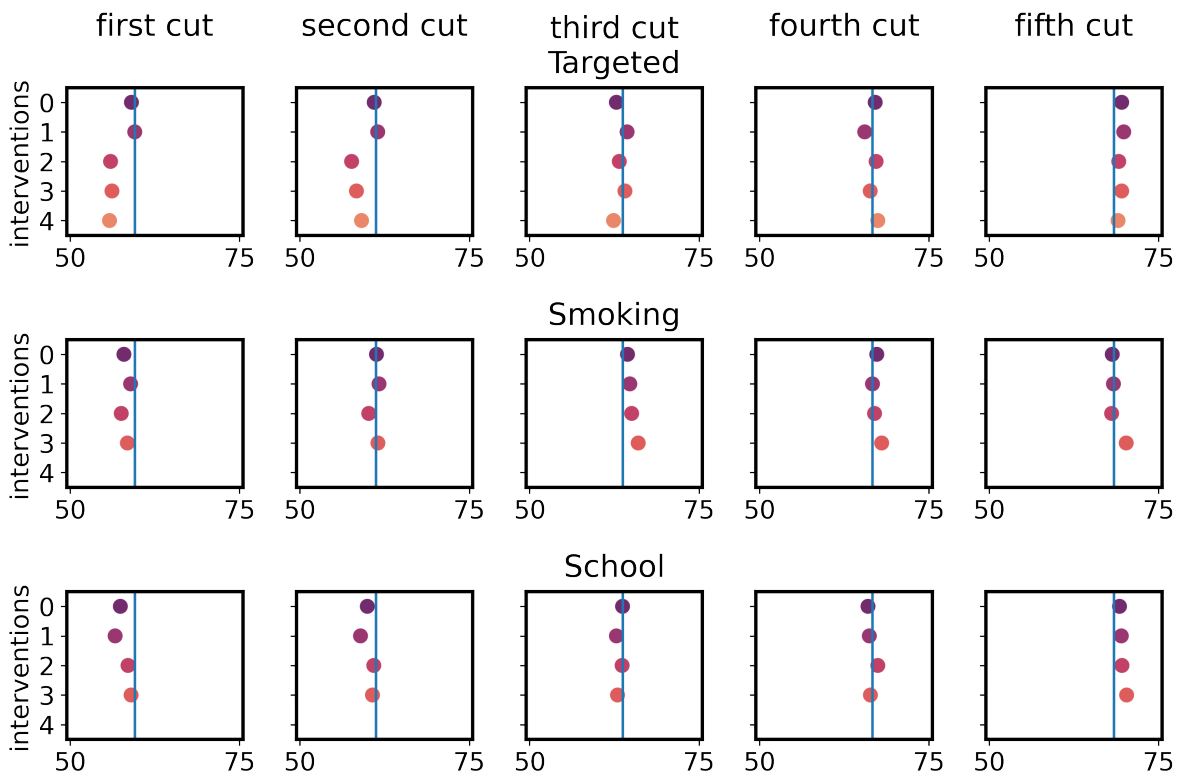

Figure D.4: The average age of women getting a MACE events when the interventions are in place in scenario 2. The first cut equals the first seven years years, the second cut the second ten years, and so on. The blue lines represent the values of the base case.

D.1.3. Scenario 3

The women in scenario 3 are more susceptible to influence from her social network. The average number of MACE events for this scenario per period are shown in Figure D.5. *School 3* is the best performing intervention in this scenario.

The performance of the different variations of the *Targeted* intervention have a varying, but small, effect on the KPI. In the first cut, variation 3, worsens the health outcome, whereas it is the best performing intervention in the remaining four cuts. The first variation, the least intensive variation, outperforms the other four variations.

The first variation of the *smoking* intervention positively affects the outcome in this scenario. Variation 4, which has the lowest frequency, but the highest duration, hardly seems to affect the KPI. Variation 2 and 4, which both have the same range of effectiveness but a different duration, do not have a substantial effect.

All *school* interventions perform bad in the last cut of scenario 3. Variation 2 and 3 do perform well in the first two cuts. Both of these are very different, as compared to variation 2, variation 3 has a lower frequency, but a higher reach.

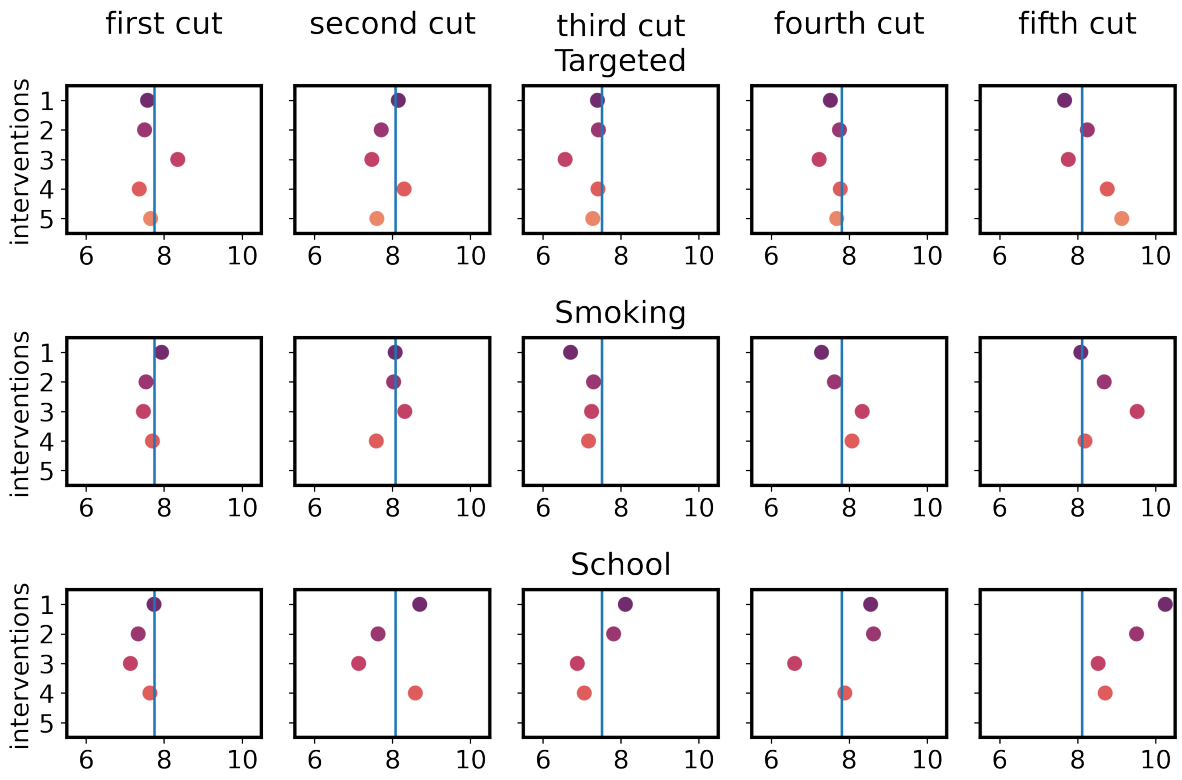

Figure D.5: The average number of MACE events when the interventions are in place in the scenario 3. The first cut equals the first seven years years, the second cut the second ten years, and so on. The blue lines represent the values of the base case.

The average age of women getting a MACE in scenario 3 is presented in Figure D.6. *School 3* which positively affected the number of MACE events, also consistently negatively affects the average age. Ideally, we have this outcome as far to the right as possible. No intervention seems to be able to really achieve this.

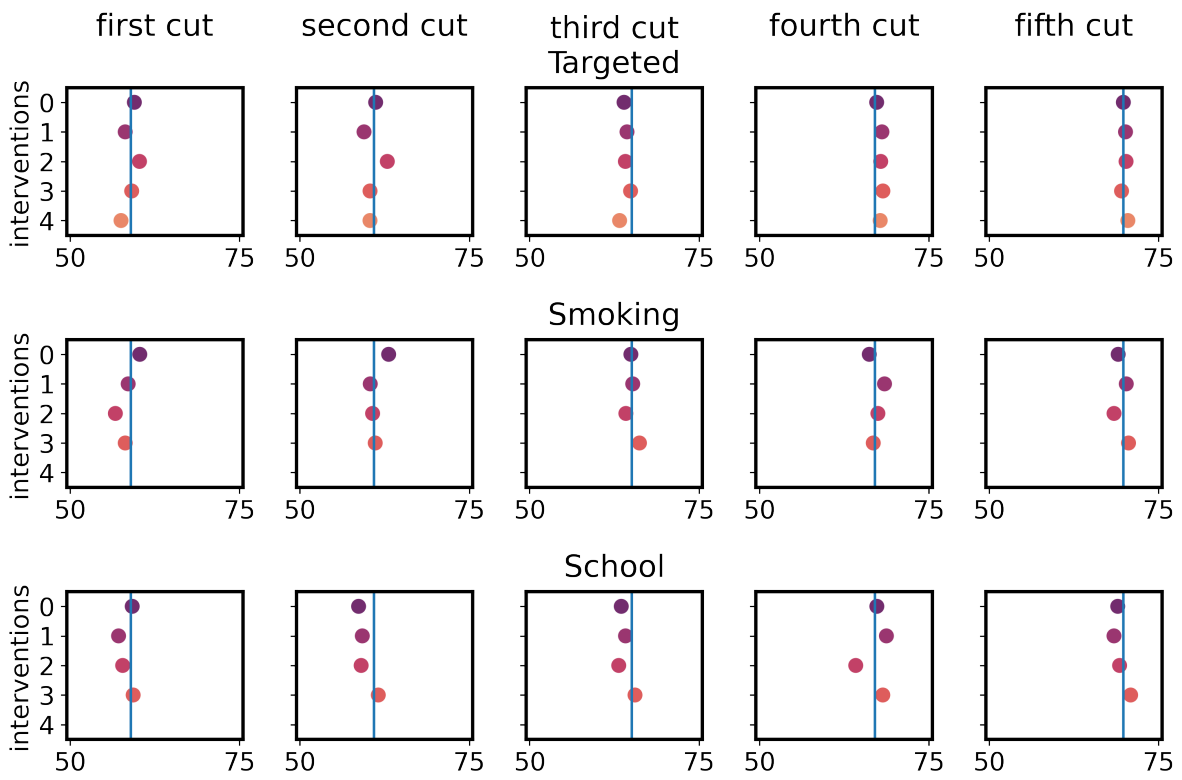

Figure D.6: The average age of women getting a MACE events when the interventions are in place in scenario 3. The first cut equals the first seven years years, the second cut the second ten years, and so on. The blue lines represent the values of the base case.

D.1.4. Discussing the differences between scenarios

All graphs of Section D.1 show that the *School*, *Smoking* and *Targeted* intervention have very little effect. All these three types of interventions have two things in common. First, they are repeating. Second, they only affect part of the female population and. None are intensive enough to really affect the health outcome. The problem is simply to resilient, possibly because the part of the population that is not affected nullifies the effect of the intervention.

The graphs also show that the KPIs may not be entirely suitable measures of performance, as there is no differentiation between a preventable MACE event (primarily due to behaviours) and MACE events due to old age.

The graphs do show that different scenarios warrant different interventions. Comparing the graphs of scenario 3 to the graphs of scenario 1. For instance, *School 4*'s has a more positive impact on scenario 1 . On the other hand, *Targeted 3* now improves the KPI for the second to fifth cuts, which it did not in scenario 1. Similarly, the *Smoking* intervention performs best in scenario 2, which assumes women are more likely to start and less likely to stop smoking.

D.2. Nuance to the second-best performing interventions overall

Figure 7.8 showed what interventions performed best on overall per scenario (based on average relative MACE per women). In this section we dissect the performances of the second best interventions per scenario. We looked at the average number of MACE events. The results are displayed in Figure D.7. As a reminder, *Smoking 3* was the second best-performing intervention in scenario 1, *Targeted 5* was the second best-performing intervention in scenario 2, and *Smoking 3* was the second best-performing intervention in scenario 3.

First of all, it is interesting to see that, since the regret score is a different method, the apparent ranking of the interventions on the scenarios as shown in section D.1 do not reflect the identified ranking

in Figure 7.8. This is because the regret score is based on overall performance, whereas these graphs from Section D.1 is more granular, as it looks at different age groups.

The blue bar represents scenario 1. In the first seven years *Smoking 3* does seem to outperform the other two interventions on the whole, but in certain age groups the other two interventions seem to result in less MACE events. This is especially noticeable in the 95+ age-group. We also see that all interventions increase the number of MACE events in this scenario. This is due to the fact that people are living healthier, and therefore getting a MACE event at an older age, so this is, essentially, something positive.

In the years 2031 to 2050 we see that for the age-groups below 54, the interventions do not really affect the outcomes, whereas for the older age-groups, the interventions do seem to improve the situation opposed to the base case. We see more staggering differences between the interventions and between the interventions and the base case in the last time period. This is especially true for the age groups of 65 year and older. With the knowledge that *smoking 3* outperforms the other two interventions in scenario 1, we can conclude that the difference between the base case and *Smoking 3* are events that were delayed because of the interventions. Note that *Targeted 5* was the fourth best-performing intervention in this scenario, so that, too, would explain the difference between the average number of MACE events between the base-case and the when this intervention is implemented.

The orange bar represents scenario 2, where women are more likely to start smoking and less likely to start smoking. *Targeted 5* was the second-best performing intervention. In the first time period, we see that this intervention always either reduces the number of MACE events or leaves it unaffected for age groups older than 45 years. It does this more so than the other interventions. In the second time period, we hardly notice an effect of any of the interventions. In the third time period, we see a big difference between the number of MACE events between both *Targeted 5* and the base case, but also between *Targeted 5* and the other interventions. We assume these events were delayed events: events that would have happened in earlier years/younger age groups in the base case, but were delayed by the intervention. *School 3* has a similar effect in the oldest age-group. However, we do know that *Smoking 3* should outperform *School 3* in the second scenario. It is also noticeable that the difference in outcomes of interventions and the outcome of the base case are less stark than in other scenarios for the older age groups.

The green bar represents scenario 3, where women are more susceptible to influence from her social network. It is, again, hard to judge how the average MACE risk that was used to calculate regret and the average number of MACE events per age group are related. *Smoking 3*, the second-best performing intervention in this scenario, significantly reduces the number of MACE events in the 85-94 age-group. We see a rise of MACE-events in the 95+ age group, implying the MACE events of people have been successfully delayed by having them stop smoking. We also see the same pattern for the other two interventions. Based on just these graphs, it is impossible to say what intervention performs best. We really need more contextual information, such as Figure 7.8.

In the second time period, the outcomes of all interventions is pretty similar to the base case, except for the age groups 55-84 and 85-94. All interventions show a reduction in the average number of MACE events for all age groups of 84 years and younger. *School 3* is an exception, which shows a small decrease in the age group 75-84. *Smoking 3* has a big impact on the number of MACE events in the oldest age group. The number of MACE events may have been partially determined by MACE events delayed by the intervention.

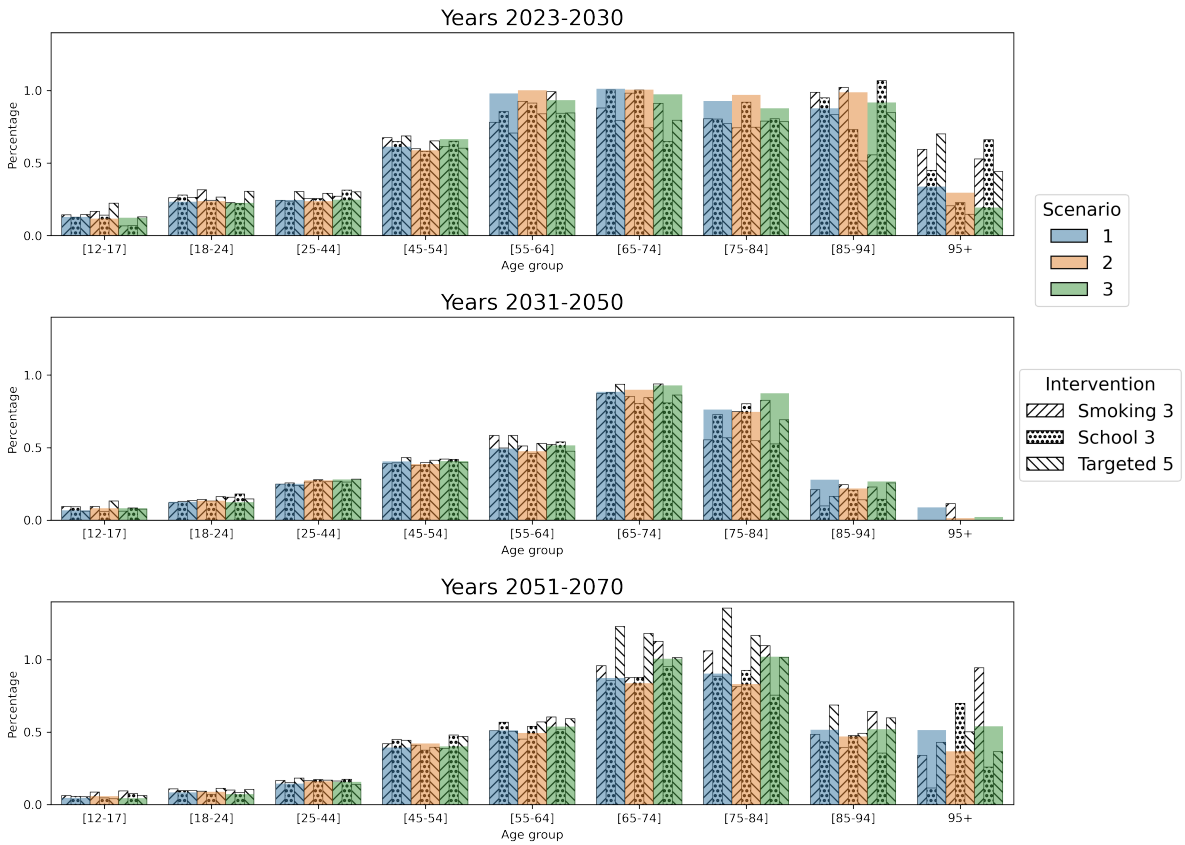

Figure D.7: A more detailed view of the interventions with the least regret in Figure 7.8. Every graph represents a different time period: The first representing the first 7 years, the second representing the following 20, and the third representing the final 20. The coloured bars in the background show the value of the base case for each scenario. The patterned bars show the values per intervention. The results are shown per age group.