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Optimizing Portfolios of Interventions for Type 2 Diabetes Prevention and Management

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Type 2 Diabetes Mellitus (T2DM), the epidemic of the 21st century, accounts for 4.6 million deaths globally and for 11% of the global health expenditure. Several different public health, primary preventive, and secondary interventions promise better health outcomes and cost savings. This paper proposes a mathematical model for T2DM that comprehends the interactions of multiple interventions, the influence of those interventions on the costs, clinical indicators and utilities of disease states, as well as population dynamics. We use the model to optimize portfolios of interventions for awareness and disease management programs for various stages of T2DM, and give insights on the different ways interventions can be beneficial. For instance, our findings suggest that the main benefit of primary prevention (in the form of awareness interventions) may shift from averting new cases to increasing screening rates under different objectives. Among other policy points, we demonstrate that an intervention which is found to be costly under the classical net present value perspective can indeed be cost-saving in the future. Thus, accounting for long-run demographics and the interaction of interventions may be a useful extension to traditional cost-utility analyses.

Key words: Health care; Type 2 diabetes mellitus; Simulation: compartmental model; Optimization: health applications


Type 2 Diabetes Mellitus (T2DM), the chronic condition named the “epidemic of the 21st century” by the International Diabetes Federation, currently affects some 366 million people globally and is expected to affect 552 million people within the next 20 years [IDF 2012]. T2DM is a metabolic disorder characterized by high blood glucose resulting from insulin resistance and relative insulin deficiency. The disease progresses slowly and T2DM is often diagnosed only after a hospitalization due to a major complication. Major complications of T2DM include coronary diseases, kidney failure and retinopathy, many of which are extremely expensive to treat, non-reversible or fatal.

The annual burden linked to T2DM is significant: 4.6 million deaths globally, a magnitude similar to the combined deaths from HIV/AIDS, malaria and tuberculosis, and over US$ 465 billion in direct costs (11% of the global health expenditure, [IDF 2012]). Currently, T2DM manifests itself with alarming prevalence rates in Gulf Cooperation Council (GCC) countries such as the United Arab Emirates (UAE) where over 20% of the population has been diagnosed with diabetes and the number with prediabetes exceeds 15% [HAAD 2011, Hajat et al. 2012]. Prevalence rates are increasing in developed countries too. For instance, in the USA diabetes prevalence has increased from 2.5% to 6.9% between 1980 and 2010 [CDC 2012].
In contrast to people with Type 1 diabetes, the majority of those with T2DM do not usually require daily insulin injections. In the initial stages of T2DM, the affected are generally prescribed a healthy diet and increased physical activity, the combination of which can stop the disease from further progression (Williams 1994). The preventable nature of T2DM and its escalating societal burden strongly motivates preventive policies to be implemented. Health authorities in many countries are actively engaging in a variety of preventive actions including general awareness campaigns, screening, and disease management programs for people diagnosed with T2DM (Gillett et al. 2010, Lancet Editorial 2010, Hajat et al. 2012).

This paper focuses on the question of how to most effectively allocate resources to a portfolio of T2DM interventions while balancing intervention spending with potential monetary savings and health benefits. To this end, we consider several different interventions: awareness campaigns for screening and averting new cases, and disease management programs in diagnosed stages for preventing disease progression.

Our main modeling contribution is exploring how costs, health benefits, and willingness to pay measures (which combines the former two Gold et al. 1996, Folland et al. 2010) can be used in a dynamic model for a chronic condition with multiple interacting interventions and long-run population dynamics. One key observation is that selecting interventions to optimize short-term objectives (e.g. discounted costs or utilities) can lead to suboptimal results in long-term objectives (e.g. long-run average costs or utilities), and vice versa.

The proposed model incorporates several novel features that support the main modeling contribution above. In particular, we establish an overarching link between various important dimensions of T2DM management: we integrate the frequency of disease management interventions and their effects on HbA1c levels (an important indicator for good blood glucose control) with increased disease progression risks in higher HbA1c stages, and the change in costs and health benefits in each stage as the disease progresses. Another novel feature is on quantifying the effect of interventions on demographic measures such as long-run population growth rates. While population growth rates are not typically included in conventional health technology analyses, they are certainly relevant for health care financing, which needs to account for not only discount rates but also for population growth trends. Additionally, we let interventions to scale in a nonlinear way, e.g. there may be marginal decreasing returns to remaining quality adjusted life years as a function of disease management intervention intensity. Our model can also incorporate the nonlinear and nonadditive interactions between costs and benefits of different interventions. Accounting for a continuum of intervention intensities allows us to consider a wider range of possible intervention levels than binary decision sets.

We derive optimal intervention levels over the set of fixed policies (those with a constant intervention levels in every time period). Fixed polices are explored for objectives such as the total discounted costs associated with direct treatment and prevention (the net present value, or NPV, which is relevant for health
care financing), quality adjusted life year (QALY) measures of community health and wellness, and willingness to pay (WTP) goals. All three objectives are explored under both open (with births and deaths) and closed (without births) population dynamics. We also explore the potential benefits of dynamic policies that can adapt the intervention policy through time as a function of the population distribution.

The main applied contribution of this paper is the use of the model to reflect the T2DM challenge in the United Arab Emirates (UAE, where the T2DM prevalence is among the highest) with published clinical, demographic and public health data. We use the model to develop new insights for the following questions that are relevant to health policy, health finance and health service provision.

- Do total discounted cost objectives lead to substantively different decisions than do objectives with sustainable long-run average objectives?
- What portfolios of interventions make sense for each of the objective functions (NPV, QALY, WTP), and how nonlinear are the costs and health benefits of such portfolios as a function of spending?
- Do policies that are optimal for criteria that account for the entire population dynamics (including births) differ from those that focus on closed cohorts of individuals in the population today?
- Which interventions should receive extra funding if additional monies were available?
- What benefits might be anticipated if one could immediately detect undiagnosed cases of prediabetes and T2DM?
- How might intervention policies influence demographic outcomes such as the population growth rate?

The responses to these questions in §4 suggest that accounting for long-run demographics and the interaction of interventions may be a useful extension to traditional cost-utility analyses and may suggest ways to improve financial and health outcomes.

1. Literature Review

Our research complements work in the areas of mathematical disease modeling in general and T2DM modeling in specific. It also complements work in the operations research literature in the area of optimization for health care policy decisions.

A number of T2DM models have been developed at the population, cohort and intra-personal levels that account for a number of risk factors and outcomes. Many of these models are calibrated using results from the United Kingdom Prospective Diabetes Study Group (UKPDS), a group that has developed a comprehensive database of risk factors for T2DM (Stratton et al. 2000, Stevens et al. 2001, Sainaghi et al. 2007, Masso-Gonzalez et al. 2009).

The Mount Hood Competition brings together computer modelers of diabetes to compare their simulation models’ performance in replicating the outcomes from published clinical trials of Type 1 and Type 2 diabetes (Mount Hood 4 Modeling Group 2007 and references therein). One of the competing models, the CORE Diabetes Model, simulates the complications of diabetes (angina, MI, congestive heart failure,
stroke, peripheral vascular disease, diabetic retinopathy, macula edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy, end-stage renal disease, neuropathy, foot ulcers and amputation) through 15 interdependent submodels (each of which is a time, state and diabetes type dependent Markov model) using Monte Carlo simulation with tracker variables to overcome the memoryless properties of standard Markov structure (Palmer et al. 2004). Another competing model, the Sheffield Diabetes Model, comprises five submodels, one for each comorbidity classification (coronary heart disease, stroke, nephropathy, retinopathy, neuropathy), and models intervention effects on several risk factors (HbA$_1c$, lipids and blood pressure) for comorbidities using risk estimates from the UKPDS Risk Engine (Stratton et al. 2000, Stevens et al. 2001).

Using the former model, Gillett et al. (2010) quantifies the effect of an education program on lifestyle modification. Their cost-utility analysis predicts the effect of lifestyle changes on incidence of complications, mortality, costs and quality of life.

The preceding articles study the effects of a single intervention. However, interventions can be bundled in a portfolio. For example, Waugh et al. (2010) notes that early screening presents a chance to offer lifestyle suggestions and treatment to people with prediabetes who would otherwise develop diabetes. Given this observation, we develop and analyze a compartmental model for optimizing a portfolio of interacting interventions in a way that is not directly amenable with typical Markov model or decision tree approaches to health economics (Brennan et al. 2006). UKPDS risk factors are included in our model in an aggregate, less detailed way than has been done in the Mount Hood Competition.

The operations management and operations research communities have also explored optimization for chronic diseases. Earlier work presents general models for screening and surveillance schedules for both infectious and non-communicable diseases (Lincoln and Weiss 1964, Lee and Pierskalla 1988). Nichols and Weinstein (1978) model the interaction of surveillance and interventions for successful treatment of hypertension using the reliability theory framework, and a serial system model. Ahmed (1978) suggests several functional forms to link the amount spent on hypertension interventions and the transition probabilities associated with them in a similar way to how we model flows below. We allow for a more flexible and even cyclical sequence of intervention, compliance, and clinical indicator states through time than in these cited works.

Some recent OR models include more disease-specific features. For example, Davies and Brailsford (2004) use simulation to explore the interaction between screening and two main diabetic eye processes. Maillart et al. (2008) use a partially observed Markov chain model to study efficient mammogram testing policies for breast cancer diagnosis, taking into account life time mortality risk, and the inconvenience/cost of mammograms. Rauner et al. (2010) introduce population level breast cancer screening policy selection as a bi-objective optimization problem given budget constraints. Some of our figures below, which plot the performance of numerous policies relative to two objectives, resemble the Pareto-optimality analysis of
Rauner et al. (2010) make novel use of a compartmental model to select over a set of alternative portfolios of interventions with projecting their effects in reducing HIV transmission.

Long and Stavert (2011) call attention to the fact that in the traditional cost-effectiveness analysis, the underlying assumption is that the intervention program costs and benefits scale linearly with investment. Among others, both Hill and Longini (2003) and Brandeau et al. (2003) note that this assumption is not valid in an infectious disease context. We extend these earlier results with demonstrating that the costs and benefits of interventions can have a non-linear structure in the noncommunicable chronic disease context, as well. Hence, we take an optimization approach rather than using the traditional cost-effectiveness analysis, which in turn enables us to consider a continuum of possible intervention portfolios.

Additional relevant demographic, clinical and intervention-related literature is found in §8.

2. Model for T2DM Prevention and Disease Management Interventions

We use a discrete-time deterministic compartmental model to describe the dynamics of T2DM in a population. With this model we optimize a portfolio of potential prevention and disease management interventions. §2.1 presents our compartmental model for T2DM progression. §2.2 describes the way that the interventions are assumed to affect T2DM progression. Financial and health objective functions are found in §2.3. §2.4 classifies policies of interest.

2.1. Disease Progression, Self-Management and Disease Control

The model is portrayed graphically in Figure 1 as a matrix of compartments. Each compartment corresponds to different combinations of disease progression, compliance with best practice, and levels of the clinical indicator HbA1c. While a more nuanced model with risk factors like age and other covariates is possible, we present this simpler model for ease of exposition. Compartments are referred to by their number (in parenthesis). The percentages give the estimated fraction of adult UAE nationals in each compartment, as described in §8.

T2DM progression is represented by a flow from left to right in Figure 1. The column at the far left represent healthy individuals in a specified population. The two compartments in that column represent two levels of risk. High risk individuals (in compartment 1) are taken to be those with significant risk factors for T2DM that are readily identifiable without complex testing (e.g., smoking or obesity). Low risk individuals (in compartment 2) are taken to be those who do not exhibit these risk factors for developing T2DM.

Undiagnosed cases may proceed to increasing levels of severity, starting with Impaired Glucose Tolerance (IGT), to Early Stage T2DM, then to Late Stage T2DM. Standard definitions for IGT and T2DM from the American Diabetes Association (ADA) are used. Namely, T2DM is defined by two-hour glucose levels of 140 to 199 mg per dL (7.8 to 11.0 mmol) on the 75-g oral glucose tolerance test (WHO 1999). A person is classified as having IGT when he/she has an intermediately raised glucose level 2 hours after the glucose
tolerance test, but to a lower level than is required to qualify for T2DM. We differentiate Late Stage from Early Stage T2DM in defining Late Stage with the presence of one or more major clinical complications of T2DM. It is possible to be undiagnosed up to the time when T2DM complications require an individual to visit a health care provider who would diagnose the underlying condition.

Once diagnosed, different levels of compliance to best practice guidelines for self-care may be observed. This is represented in the compliant and non-compliant columns for each diagnosed stage in Figure 1, with compliant columns on the right and non-compliant columns on the left.

The three rows in diagnosed groups correspond to the degree to which compliance results in better control of clinically relevant measures (glycemic control measured by HbA1C levels). In order to be consistent with data from Al-Kaabi et al. (2008), good glycemic control is defined here to be an HbA1C level of less than 7%, fair glycemic control is defined to be an HbA1C level of at least 7% but less than 8%, and poor glycemic control is defined to be an HbA1C level of at least 8%. Hence, there are six compartments for each of the three diagnosed stages (IGT, Early and Late Stage).

This summarizes the nature of the $N_C = 23$ compartments of the model. In order to describe the number of individuals in each compartment through time, we let $x_{i,t}$ denote the number of individuals in the modeled population that are in compartment $i$ at time $t$, for $i = 1, 2, \ldots, N_C$ and $t = 0, 1, \ldots$. We define $x_t = (x_1, t, x_2, t, \ldots, x_{N_C}, t)$ so that $|x_t| = \sum_{i=1}^{N_C} x_{i,t}$ is the population size at time $t$.

We now describe the dynamics of flows into and out of the compartments through time. We first describe the open population (with births and deaths) dynamics before describing the closed population (without
births) dynamics.

Deaths can occur from any compartment. The column vector $\mathbf{d}$ denotes the corresponding death rate from each compartment. We denote by $\mathbf{b}$ the matrix of birth rates, where $b_{ij}$ denotes the birth rate into $i$ per individual in compartment $j$. If entry to the modeled population occurs at the time of actual birth then one might set $b_{ij}$ to 0 for $i \geq 3$. If entry occurs at an older age, e.g. when an individual is first responsible for his/her own health insurance, then $b_{ij}$ may also exceed 0 for other compartments.

Permissible flows between compartments are denoted with arrows in Figure 1. The arcs corresponding to births and deaths are ignored in Figure 1 for simplicity. The flow rate of an individual in compartment $j$ to compartment $i$ at time $t$ is denoted $f_{i,j,t}$. Flow rates at time $t$ are assumed to be a function of decisions $z_t$ on T2DM interventions as described further in §2.2. Here, we presume that further advancement of the disease stops for people with $\text{HbA}_1c \leq 7\%$. Compliance provides a slower rate of advancement than does non-compliance. Further details on the flow rates can be found in §8.

With this framework, the dynamics of population levels of T2DM can be modeled as a first order linear dynamical system. We assume the following sequence of events in each time period $t$:

1. births and deaths, as modeled by a matrix $\mathbf{B}_t$,
2. horizontal flows (disease stage transitions, level of compliance), as modeled by a matrix $\mathbf{H}_t$,
3. vertical flows (clinical indicator transitions) for remaining individuals, as modeled by a matrix $\mathbf{V}_t$.

Here, we set $\mathbf{B}_{i,j,t} = b_{i,j}$ for $i \neq j$ and $\mathbf{B}_{i,i,t} = 1 + b_{i,i} - d_i$, and observe that $\|\mathbf{B}_t \mathbf{x}_t\|_1$ is the total population size at time $t+1$. Both $\mathbf{H}_t$ and $\mathbf{V}_t$ are probability transition matrices (their columns add to 1) with probabilities that are determined by the $f_{i,j,t}$ for horizontal and vertical flows, respectively. Let $\circ$ be the Hadamard product, so that the $ij$th element of $\mathbf{H}_t \circ \mathbf{V}_t$ is $\mathbf{H}_{i,j,t} \mathbf{V}_{i,j,t}$. Thus, the diagonal and non-diagonal parts of $\mathbf{H}$ can be separated as in $\mathbf{H}_t = (I \circ \mathbf{H}_t) + (\mathbf{H}_t - I \circ \mathbf{H}_t)$. The vertical and horizontal flows in between compartments can be represented by the probability transition matrix $\mathbf{F}_t = \mathbf{V}_t(I \circ \mathbf{H}_t) + (\mathbf{H}_t - I \circ \mathbf{H}_t)$.

With the above sequence of events for births, deaths and other flows, the one-step transition dynamics are linear with transition matrix $\mathbf{P}_t = \mathbf{F}_t \mathbf{B}_t$ and

$$\mathbf{x}_{t+1} = \mathbf{P}_t \mathbf{x}_t \text{ for } t = 0, 1, \ldots$$

(1)

The open population dynamic in (1) includes birth and death rates as well as disease state dynamics.

It is also interesting to examine health economic outcomes for a given set individuals in a population without accounting for new entrants to the population (a closed population). To do this, we define $\tilde{\mathbf{B}}_t$ where $\tilde{\mathbf{B}}_{i,j,t} = 0$ for $i \neq j$, and $\tilde{\mathbf{B}}_{i,i,t} = 1 - d_i$, and $\tilde{\mathbf{P}}_t = \mathbf{F}_t \tilde{\mathbf{B}}_t$. For the individuals in the population at time 0, the closed population dynamic is described with the following one-step transition,

$$\mathbf{x}_{t+1} = \tilde{\mathbf{P}}_t \mathbf{x}_t \text{ for } t = 0, 1, \ldots$$

(2)
2.2. Interventions

A number of activities may be undertaken in order to reduce the overall burden of T2DM by modifying the population dynamics of the disease. Here we consider four interventions: general awareness campaigns that encourage both healthier lifestyles and increase screening rates \((k = 1)\); as well as targeted coaching activities to those diagnosed with IGT, Early Stage, and Late Stage \((k = 2, 3, 4\), respectively). The intensity (or frequency) of intervention \(k\) in time period \(t\) is denoted \(z_{k,t}\), and the marginal cost per person of \(z_{k,t}\) is denoted \(C_k(z_{k,t})\). Fixed costs of disease management programs can be modeled separately. A change in the intensity or frequency of an intervention may influence the flow rates of one or more of the flows \(f_{i,j,t}\).

Because an awareness campaign targets the general population, we model the overall expenditure of such programs, with \(z_{1,t}\) contacts per person per time period, as \(C_1(z_{1,t})||x_t||_1\). The cost of coaching sessions (interactions between health care providers and people with diabetes) is assumed to apply to individuals that have been diagnosed in a given stage, so that if \(z_{k,t}\) sessions are provided in period \(t\), the total cost is \(C_k(z_{k,t})\sum_{t=1}^{T} x_{k,t}\), where the sum is the number of diagnosed individuals in the compartments to which the intervention applies \((k = 2, 3\) and \(4\) for IGT, Early Stage and Late Stage T2DM, respectively).

We let \(z_t = (z_{1,t}, z_{2,t}, z_{3,t}, z_{4,t})\) denote the vector of decision variables at time \(t\). A policy \(z_* = (z_0, z_1, \ldots, z_{\tau-1})\) is a sequence of choices for \(z_t\) for all \(t\) for \(\tau\) periods, where \(\tau\) may be a positive integer or may be infinite to reflect an arbitrarily long planning horizon. The set of feasible \(z_t\) is taken to be \(z_t \geq 0\) (additional constraints may apply in other specific contexts). The total cost of interventions in period \(t\) is

\[
C(z_t)Bx_t,
\]

where \(z_t\) is a vector of intervention decisions, \(C(z_t)\) the vector of per capita costs of interventions in period \(t\), and \(B\) is a suitably defined matrix of zeros and ones.

In the numerical study in §4, an increase in \(z_{1,t}\) increases the flow rate into the healthy low risk compartment and increases the flow rates from undiagnosed compartments into diagnosed compartments. An increase in \(z_{k,t}\) for \(k = 2, 3, 4\) increases flows into compliant compartments and thereby result in lower (improved) \(\text{HbA}_{1c}\) levels for the populations that they target. Consequently, an increase in \(z_{k,t}\) (for \(k = 2, 3\)) also decreases flows to more advanced stages of T2DM.

2.3. Different Relevant Performance Objectives

Different objective functions to evaluate the performance of an intervention policy \(z_*\) may include financial objectives (e.g., the NPV of intervention and treatment costs), health objectives (e.g., QALYs) and willingness to pay objectives which combine financial and health objectives. Both discounted and long-run average performance objectives might be considered. This section describes how we account for these objectives.
Expenditures due to T2DM include the cost of interventions that were outlined in §2.2 and treatment costs (blood glucose measurement devices and consumable strips, regular primary care visits associated with full compliance, drugs, insulin, etc.; costs due to T2DM-related complications). We denote the average annual cost of treatment and complications per person in compartment $i$ by $c_i$, and set $c' = (c_1, c_2, \ldots, c_{NC})$.

**Discounted objective functions with open population dynamics.** We first examine the total discounted financial burden of T2DM at a population level including costs due to future births. Assuming a discount factor of $\beta \in [0, 1)$, and an initial population $x_0$, the total discounted cost in $\tau$ periods due to treatment plus the cost of interventions is

$$J_{S,\tau}(z) = \sum_{t=0}^{\tau-1} \beta^t (c' + C(z)B)x_t.$$  (3)

The total discounted cost depends on the population size in each compartment in each period. The population vector $x_t$ at time $t$ depends upon the transition matrices $P_{t-1}, P_{t-2}, \ldots, P_0$ and the initial population $x_0$. The transition matrices $P_t$ may depend on $z_t, x_t$ and $t$.

We denote by $z^*_{\lambda,\tau}$ a policy that minimizes the total discounted cost over a time horizon $\tau$, i.e., with

$$J_{S,\tau}(z^*_{\lambda,\tau}) = \inf_{z \geq 0} J_{S,\tau}(z),$$  (4)

when such a policy exists and is unique. We found unique optima in numerical examples.

Health outcomes are another objective of interest. One common measure of health and wellness is the QALY (Gold et al. 1996). We let $q_i$ be the QALY per life year per person in compartment $i$, and set $q$ to be the vector of those values. The total discounted QALYs from a policy $z$ over $\tau$ time periods is

$$J_{QALY,\tau}(z) = \sum_{t=0}^{\tau-1} \beta^t q' x_t.$$  (5)

Financial outcomes and health outcomes can be combined with a willingness to pay (WTP) parameter $\lambda$. Essentially, QALYs are monetized at the rate of $\lambda$ units of currency per QALY. This motivates a discounted WTP objective function

$$J_{\lambda,\tau}(z) = J_{S,\tau}(z) - \lambda J_{QALY,\tau}(z).$$  (6)

Different policies may be optimal for different levels of $\lambda$.

We denote optimal policies to minimize $J_{QALY,\tau}(z)$ and $J_{\lambda,\tau}(z)$, when they exist, by $z^*_{\lambda,\tau}$ and $z^*_{\lambda,\tau}$.

**Discounted objective functions for closed populations.** The above objectives are readily adapted to account for cost and health outcomes for a closed population at time 0 (without accounting for births). We denote those objectives with a tilde on the relevant objective function. For example, we write

$$\tilde{J}_{S,\tau}(z) = \sum_{t=0}^{\tau-1} \beta^t (c' + C(z)B)x_t,$$  (7)

where the state dynamic is described by $x_{t+1} = P_t x_t$, as in (2). We similarly write $\tilde{J}_{S,\tau}$ and $\tilde{J}_{QALY,\tau}$ for the QALY and WTP objectives and a closed population.
Average-performance objective functions. The above objectives are based on discounted streams of costs and benefits. Average costs and benefits may also be of interest, especially for long-run performance objectives. For each of the above discounted objective functions, we denote the corresponding average performance objective function with a $V$ rather than a $J$. For example, the average financial cost of treatment and interventions is denoted by

$$V_{\ell,\tau}(z) = \frac{1}{\|x_0\|_1} \sum_{t=0}^{\tau-1} \left( c' + C(z)B \right) x_t \|x_t\|_1,$$

for finite $\tau$. Similarly, we define $V_{QALY,\tau}(z)$ and $V_{\lambda,\tau}(z)$ for average health and WTP in an open population.

We define $\tilde{V}_{\ell,\tau}(z)$ for $\ell \in \{\$, QALY, $\lambda\}$ to model the total undiscounted cost and health benefits per person in a closed population beginning at time 0 (thus the $\tilde{\cdot}$, as was done for $\tilde{J}$), but model total costs or benefits of the population for time $\tau$ or death, whichever occurs first, rather than average costs. For example,

$$\tilde{V}_{\$,\tau}(z) = \frac{1}{\|x_0\|_1} \sum_{t=0}^{\tau-1} \left( c' + C(z)B \right) x_t,$$

with the closed population dynamic $x_{t+1} = \bar{P}(z_t)x_t$.

We will refer to a policy that achieves the minimum (or infimum), over all feasible $z_\ast$, of objective function for figure of merit $\ell \in \{\$, QALY, $\lambda\}$ and type $\eta \in \{J, \tilde{J}, V, \tilde{V}\}$ when it exists (such an optimum is typically unique in numerical experiments below). For example, $z_\ast^{V_{\$,\tau}}$ would be a policy that minimizes the long-run average cost objective in (8). We allow $\tau = \infty$ in the objective functions above to denote the limiting case as $\tau \to \infty$, when the relevant limit exists.

Demographic measures, such as the average lifespan and the long-run population growth rate, are also of interest. Such demographic figures of merit are further explored in §3 below.

2.4. Classes of Policies

It will be useful to classify policies $z_\ast$ in two different ways. One way to classify policies is with respect to traditional nomenclature in dynamic programming literature. A policy $z_\ast$ is called a fixed policy if $z_t = z$ for some $z$ for all $t$. Fixed policies are interesting in that the total cost of interventions per person is constant, independent of $x_t$ and time. A stationary policy requires that $z_t$ not depend on $t$, although it may depend on $x_t$. Fixed policies provide input for aggregate capacity decisions. The implementation of a stationary policy that depends on $x_t$ would additionally require information about shifts in the health status of individuals in the population through time.

A second way to classify policies is to examine the effect of the policy on the long-run population size and costs. We define a policy $z_\ast$ to be a costly policy for which $J_{\$,\infty}(z_\ast) = \lim_{\tau \to \infty} J_{\$,\tau}(z_\ast)$ does not exist because the infinite horizon discounted cost is infinite.

We define a policy to be a shrinking policy if the policy ultimately leads to a long-run decline in the population size. More formally, a policy $z_\ast$ is said to be shrinking if, for any given constant $A$ and initial state $x_0$, there is a time $t_{A,x_0}$ such that the total population size is less than $A$, or $\|x_t\|_1 < A$, for all $t \geq t_{A,x_0}$.
We define a policy to be sustainable if it is not costly and the total population size never goes below a certain threshold. More formally, a policy \( z \) is said to be sustainable if, for some initial state \( x_0 \), there is an \( A' > 0 \) such that \( \| x_t \| > A' \) for all \( t = 0, 1, \ldots \), and the policy is not costly.

When optimizing the infinite horizon versions (\( \tau \to \infty \)) of any of the objective functions in §2.3, we will be optimizing from the set of costly and sustainable policies, but will not consider shrinking policies to be feasible for reasons of acceptability to a decision maker. Although the classification of policies as costly, shrinking and sustainable is not exhaustive for dynamic policies, we will show they are mutually exclusive and exhaustive for fixed policies in §3.

3. Analysis For Fixed Policies

The optimal policy for a given objective function in §2.3 (discounted or undiscounted; open or closed populations; financial, health or WTP) may be state dependent, and therefore difficult to compute and to implement. We therefore analyze the optimal policy within the simpler-to-study class of fixed policies in this section. Because of the time and state invariance of fixed policies, we drop \( t \) from subscripts (\( f_{i,j}, P_{i,j}(z) \), etc.) in this section for notational convenience.

**Fixed policies and the Perron-Frobenius theorem.** If \( z_t = z \) for all \( t \) for a given fixed \( z \), then a policy is defined by \( z \), (3) simplifies considerably because \( P(z) \) is time invariant, and \( x_t = (P(z))^t x_0 \) by (1). Because \( P(z) \) is a nonnegative square matrix it is natural to turn to Perron-Frobenius theory for structural results.

We first recall some properties of matrices. A matrix \( A \) is said to be irreducible if \( A \) is not reducible (i.e., admits no permutation of its indices that transforms it into a block triangular matrix, [Meyer and Meyer 2001, p. 671]). A non-negative irreducible matrix \( A \) is called primitive if it has only one eigenvalue on its spectral circle [Meyer and Meyer 2001, p. 674]. A sufficient condition for \( A \) to be primitive is to have at least one non-zero diagonal element besides being irreducible [Meyer and Meyer 2001, p. 678].

Recalling Figure 1 and the application context, we hypothesize that Perron-Frobenius theory will apply if Assumption 1 below holds. This hypothesis is confirmed by Lemma 1.

**Assumption 1.** For a given \( z \), there exists a compartment \( i \) such that (i) at least one compartment \( i \) has a positive birth rate, meaning \( b_{i,j} > 0 \) for all \( j \), (ii) \( F_{i}(z) > 0 \) for that \( i \), (iii) all \( N_C \) compartments in Figure 1 are reachable from \( i \) using arcs with positive transition rates (of the form \( P_{i,j} > 0 \)).

**Lemma 1.** If Assumption 1 holds for \( z \) then \( P(z) \) is non-negative, irreducible and primitive.

Assumption 1 holds for all \( z \) of interest in applications in §4 below, as can be verified by checking the death rates, the choice \( i = 1 \), and the functional forms of the \( f_{i,j} \). Thus, the Perron-Frobenius theorem for nonnegative matrices is applicable for fixed policies for our problem. We recall here a strong statement of the Perron-Frobenius theorem (see [Hill and Longini 2003]).
Theorem 1 (Perron-Frobenius Theorem). Let $A$ be a non-negative irreducible matrix and let $\rho(A)$ denote its spectral radius.

1. $\rho(A) > 0$ and $\rho(A)$ is an eigenvalue of $A$.
2. $\rho(A)$ can be associated strictly positive left and right eigenvectors. This is the only eigenvalue for which this happens.
3. If $\xi$ is any other eigenvalue of $A$ then $|\xi| \leq \rho(A)$.
4. $\rho(A)$ has multiplicity 1 (it is a simple eigenvalue).
5. If $0 \leq B \leq A$ and $\xi$ is an eigenvalue of $B$, then $|\xi| \leq \rho(A)$. If $|\xi| = \rho(A)$, then $B = A$, so that $\rho(A)$ increases when any element of $A$ increases.

[1] Hill and Longini (2003) further note that if $A$ is strictly positive then part 3 can be strengthened to $|\xi| < \rho(A)$, and that this result also holds for non-negative primitive $A$. Then, there exists a real positive eigenvalue (Perron-Frobenius eigenvalue or Perron root), which is strictly greater in absolute value, then other eigenvalues, hence it is the dominant eigenvalue (spectral radius) of $A$.

This has several important consequences for the long-run demographics of the population.

Lemma 2. For any $z$ that satisfies Assumption 7 (i) $P(z)$ has a dominant eigenvalue, $r_{0,z}$, that has multiplicity 1 and is greater in magnitude than all other eigenvalues of $P(z)$; (ii) the long-run population growth rate with $P(z)$ is $100(r_{0,z} - 1)$%; (iii) the right eigenvector $v_{0,z}$ associated with $r_{0,z}$ is strictly positive; (iv) the long-run fractions of individuals in each compartment is $\lim_{t \to \infty} x_i / \|x_i\|_1 = v_{0,z} / \|v_{0,z}\|_1$.

Thus we can assume that $v_{0,z}$ is scaled so that $\|v_{0,z}\|_1 = 1$, and we do so in the rest of the paper.

Fixed policies and objective functions with discount factors. The infinite horizon discounted cost of disease management and interventions in Equation (3) (as $\tau \to \infty$) simplifies considerably with a fixed policy because $P(z)$ is time invariant and $x_i = P(z)^t x_0$. For a fixed policy,

$$J_{S,\infty}(z) = \sum_{t=0}^{\infty} \beta^t (c^t + C(z)B x_0) = (c^t + C(z)B)(I - \beta P(z))^{-1} x_0$$

where $I$ is the identity matrix, when the inverse $(I - \beta P(z))^{-1}$ exists.

The infinite horizon discounted QALY and WTP objective functions have similar simplifications, with $J_{QALY,\infty}(z) = q(I - \beta P(z))^{-1} x_0$ and $J_{d,\infty}(z) = (c^t + C(z)B - \lambda q^t)(I - \beta P(z))^{-1} x_0$. The values of $J_{S,\infty}$, $J_{QALY,\infty}$, and $J_{d,\infty}$ evaluated for a fixed policy can be found with similar formulas that substitute $P(z)$ for $P(z)$.

The expression $(I - \beta P(z))^{-1}$ suggests a mechanism to characterize policies with respect to their performance on infinite horizon discounted costs. If the infinite horizon cost $\sum_{t=0}^{\infty} (\beta P(z))^t$ diverges, then the inverse $(I - \beta P(z))^{-1}$ does not exist. Given that $P(z)^t x_0$ is on the order of $r_{0,z}^t v_{0,z}$, such divergence occurs if and only if $\beta r_{0,z} \geq 1$. Thus, the set of policies for which the infinite horizon discounted cost diverges, $\mathcal{S}_1 = \{z : z \geq 0, \beta r_{0,z} \geq 1\}$, consists of costly policies.

One can also show that the set of policies $S_2 = \{ z : z \geq 0, r_{0,x} < 1 \}$ consists of shrinking policies. Shrinking policies are not costly because $\beta < 1$ and $r_{0,x} < 1$ imply that $\beta r_{0,x} < 1$, and costly policies are not shrinking because $\beta r_{0,x} \geq 1$ implies that $r_{0,x} \geq 1/\beta > 1$.

We define $S_3 = \{ z : z \geq 0, r_{0,x} \geq 1, \beta r_{0,x} < 1 \}$ to be the set of all other fixed policies. One can verify that a policy $z \in S_3$ is sustainable by noting that the choice of $x_0 = \nu_{0,z}$ results in a population whose size never falls below $\|x_0\|_1$ and that $J_{\delta,\infty}(z)$ is finite because $\beta r_{0,x} < 1$ (and arguments like those in the proof of Lemma 2). These arguments justify the following lemma.

**Lemma 3.** A fixed policy $z$ that satisfies Assumption [1] is (i) costly iff $z \in S_1 = \{ z : z \geq 0, \beta r_{0,x} \geq 1 \}$; (ii) shrinking iff $z \in S_2 = \{ z : z \geq 0, r_{0,x} < 1 \}$; (iii) sustainable iff $z \in S_3 = \{ z : z \geq 0, r_{0,x} \geq 1, \beta r_{0,x} < 1 \}$.

Because we do not consider shrinking policies to be feasible, a policy $z^{<\delta,\infty}$ is an optimal fixed policy if

$$J_{\delta,\infty}(z^{<\delta,\infty}) = \inf_{z \in S_3} J_{\delta,\infty}(z).$$

(11)

**Fixed policies and long-run average cost objectives.** The long-run average objective functions in §2.3 also simplify with fixed policies. In particular, techniques like those used to prove Lemma 2 indicate that the long-run average annual per capita cost of disease maintenance, treatment and interventions for a fixed policy $z$ is:

$$V_{\delta,\infty}(z) = (c' + C(z)B)\nu_{0,z}.$$  

(12)

From (12) we see that an optimal policy for long-run average per capita costs, $z^{<\delta,\infty}$, depends on the long-run population distribution but not on the initial state of the population, $x_0$. This differs from the case of infinite horizon discounted costs – (10) highlights the explicit dependence of $z^{<\delta,\infty}$ on $x_0$.

Similar simplifications are available for the long-run average QALYs per capita per year for a fixed policy $z$, $V_{QALY,\infty}(z) = q'b'\nu_{0,x}$ and the long-run average WTP per capita per year, $V_{\delta,\infty}(z) = (c' + zB - \lambda q')\nu_{0,x}$.

**Fixed policies and other demographic measures.** In addition to costs and QALYs, there are other demographic measures that may be of interest to a policy maker. One is the long-run population growth rate, which by Lemma 2 is a $100(r_{0,x} - 1)%$ increase in population annually. Another interesting demographic measure is the average life expectancy for a given population. For fixed policies, the expected remaining life years, conditional on starting in any given compartment, can be determined for a given fixed policy $z$ with standard linear algebra techniques similar to those used above. These demographic measures are often outside of the scope of a typical cost utility analysis yet are relevant for public health planning.

### 4. Numerical Experiments with Fixed Policies and Policy Implications

This section uses the model above in a numerical example that is based on parameter estimates for T2DM progression and the population distribution of Emirati nationals. We use that model to gain insights for policy decisions for portfolios of interventions, as well as to explore the interactions of interventions with
respect to the several relevant performance objectives. This section focuses on the class of fixed policies as it responds to the key policy questions that were listed in the introduction to the paper.

The model has many parameters, and some parameters are better known than others. Where possible, point estimates were made based on published or stakeholder data on clinical and demographic parameters, with priority given to data from the UAE or GCC states. To the best of our knowledge, data regarding the influence of interventions directly on flow rates is not readily available from any geography. We therefore assumed S-shaped logistic curves for flow rates as a function of intervention intensities. We fitted the parameters of those logistic models to reflect findings in the literature on HbA$_{1c}$ change as a function of intervention intensity. The fitting process required making an assumption about current intervention levels, $z_{\text{base}}$. For the numerical examples here we presumed $z_{\text{base}} = [.3 .3 .3 .3]'$. More details of the parameter fitting process are in §8.

The discount factor was set to $\beta = 0.95$ and the WTP threshold was set to $\lambda = 50K$ US$/QALY$ unless otherwise specified. We normalized the initial population size $x_0$ to 1 so that objective function values reported for discounted figures of merit (with $J$ or $\tilde{J}$) are per person at time 0.

4.1. How do optimal policies for different performance objectives influence outcomes?

This section computes the optimal fixed policies for several objective functions of interest and provides an understanding of the behavior of the objective functions with respect to changes in intervention intensities.

Nonlinearity of cost and health benefits in intervention values. Figure 2 shows the infinite horizon discounted cost $J_{\$,\infty}(z)$ for the fixed policy $z = (z_1, z_2, z_3, z_4)$ as a function of $z_1$ and $z_2$ when the other decision variables are set to their optimal values ($z_3 = z_{3,J_{\$,\infty}}$ and $z_4 = z_{4,J_{\$,\infty}}$). The values of $z_1$ and $z_2$ that minimize $J_{\$,\infty}(z)$ are $z_{1,J_{\$,\infty}} = 0.0$ and $z_{2,J_{\$,\infty}} = 1.368$. This objective function appears to be smooth but is not linear and is not unimodal. A local minimum is near $z_1 \approx 4, z_2 \approx 1.4$.

Figure 3 demonstrates another view on the nonlinearity of cost benefit ratios for interventions. The dots in Figure 3 represent the average remaining quality adjusted life expectancy $\tilde{V}_{QALY,\infty}$ (beyond 18 years of age) and the average cost of intervention and treatment $\tilde{V}_{\$,\infty}$ (per person in the population at time 0). Each point corresponds to an evaluation of these objective functions for the optimal undiscounted WTP policy, $z_{\*,\tilde{V}_{\$,\infty}}$, for $\lambda = 0, 1K, \ldots, 100K$ US$/QALY$. Low values of $\lambda$ result in lower values of $\tilde{V}_{QALY,\infty}$ and $\tilde{V}_{\$,\infty}$. As $\lambda$ increases (as health benefits are valued more) $\tilde{V}_{\$,\infty}$ increases much faster than $\tilde{V}_{QALY,\infty}$, and there is a vertical asymptote near the point where $\tilde{V}_{QALY,\infty}$ cannot be increased further (life can not be prolonged forever even with infinite spending).

Policy point: The benefits of a given intervention are nonlinear. The shape of the nonlinearity of costs and benefits of a given intervention is not always monotonic (may have increasing or decreasing marginal returns, depending on the values of the other interventions). As a result, separately optimizing the level of each intervention sequentially may result in a poorer performance than does optimizing interventions jointly as a portfolio (the effect is stronger for $V_{\$,\infty}$ than for $J_{\$,\infty}$, data not shown).
Figure 2  $J_{S,\infty}$ is Multimodal in $z_1$ and Appears to be Convex in $z_2$.

Figure 3  $\tilde{V}_{S,\infty}$ Increases Faster than $\tilde{V}_{QALY,\infty}$ as $\lambda$ Increases.

Table 1  Optimal Fixed Policies.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>$z^{*-J_{S,\infty}}$</th>
<th>$z^{*-J_{\lambda,\infty}}$</th>
<th>$z^{*-V_{S,\infty}}$</th>
<th>$z^{*-V_{\lambda,\infty}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Awareness Coverage</td>
<td>0.0000</td>
<td>21.2241</td>
<td>4.1854</td>
<td>13.8576</td>
</tr>
<tr>
<td>IGT Coaching</td>
<td>1.3684</td>
<td>2.5894</td>
<td>1.6187</td>
<td>2.5299</td>
</tr>
<tr>
<td>Early Stage Coaching</td>
<td>1.2398</td>
<td>2.6265</td>
<td>1.4536</td>
<td>0.0000</td>
</tr>
<tr>
<td>Late Stage Coaching</td>
<td>0.2761</td>
<td>2.4191</td>
<td>0.0003</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Performance of optimal policies for different objective functions, health outcomes and demographics. A number of interesting observations can be made by comparing the policies that are optimal for the different objective functions (in the class of fixed policies) and the outcomes that are associated with these policies.

Table 1 displays intervention levels of the optimal policies in columns for both discounted and long run average performance for both financial and WTP (with $\lambda = 50K$ US$/QALY$) objectives. The optimal level of general awareness intervention is 0 for $J_{S,\infty}$ and 4.18 for $V_{S,\infty}$, which suggests that the general awareness effort modeled here is not cost-effective from a pure financial (discounted NPV of disease burden) perspective but it is effective from another financial perspective: that of long-run average cost per capita.

Policy point: General awareness is cost-effective at the $\lambda = 50K$ US$/QALY$ level but not cost saving from the perspective of the $J$ objective. With a long-run average perspective ($V$), general awareness is both cost effective and cost saving. General awareness can have long-range benefits that are not weighted as heavily by a discounted perspective.

Not surprisingly, a comparison of $z^{*-J_{S,\infty}}$ with $z^{*-J_{\lambda,\infty}}$ indicates a greater emphasis on general awareness and other interventions when health benefits are valued to a greater extent. A similar increase in prevention and IGT interventions is also observed for the long-run average objectives (rightmost two columns).

The optimal long-run average policies do not invest as much in interventions for diagnosed diabetics...
Table 2: Objective Function Values and Demographic Outcomes for Optimal Fixed Policies.

<table>
<thead>
<tr>
<th></th>
<th>$z = 0$</th>
<th>$z^{base}$</th>
<th>$z^{J_{5,\infty}}$</th>
<th>$z^{J_{L,\infty}}$</th>
<th>$z^{V_{5,\infty}}$</th>
<th>$z^{V_{L,\infty}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$J_{5,\infty}$</td>
<td>26186</td>
<td>26150</td>
<td>25596</td>
<td>32988</td>
<td>27408</td>
<td>30716</td>
</tr>
<tr>
<td>$J_{L,\infty}$</td>
<td>-1231300</td>
<td>-1241900</td>
<td>-1249400</td>
<td>-1358100</td>
<td>-1311200</td>
<td>-1331100</td>
</tr>
<tr>
<td>$V_{5,\infty}$</td>
<td>824.7445</td>
<td>807.5611</td>
<td>762.7717</td>
<td>811.915</td>
<td>645.3736</td>
<td>740.8355</td>
</tr>
<tr>
<td>$V_{L,\infty}$</td>
<td>-46386</td>
<td>-46577</td>
<td>-46862</td>
<td>-48787</td>
<td>-48616</td>
<td>-48852</td>
</tr>
</tbody>
</table>

Low Risk 0.2921 0.3000 0.2898 0.7395 0.4069 0.6875
High Risk 0.2666 0.2600 0.2645 0.0055 0.1904 0.0371
Undiagnosed 0.3023 0.2726 0.2959 0.0075 0.0163 0.0082
IGT 0.0619 0.0878 0.0997 0.2120 0.3215 0.2339
Early 0.0346 0.0398 0.0130 0.0037 0.0627 0.0290
Late 0.0424 0.0398 0.0371 0.0010 0.0021 0.0044
HbA1c 8.1427 7.7020 7.0465 6.7777 6.8061 6.9336
QALY 0.9442 0.9477 0.9525 0.9920 0.9852 0.9919
Growth Rate 1.3275% 1.3617% 1.3745% 1.7419% 1.5961% 1.7011%

(early and late stage) as the discounted objective functions require. This appears to be because of the emphasis on prevention, as can be seen in Table 2. That table gives the objective function values for the four objective functions for each of the four optimal policies in Table 1. Table 2 also gives the long-run fraction of individuals in a variety of states (low risk, high risk, undiagnosed, IGT, early and late stages) as well as the long-run average HbA1c for diagnosed individuals, the long-run average QALY per person per year, and the long-run population growth rate associated with each policy. These figures of merit are also displayed for the policy of “doing nothing” ($z = 0$) and “current” ($z^{base}$) intervention levels. The bold values of the objective functions can be used to validate that the claimed optimal policy indeed performs better than the other policies with respect to the objective function it optimizes.

From Table 2 we see that the infinite horizon cost of interventions and treatments per person in the population at time 0 is US$ 25,596, a figure that is $(27,408 - 25,596) / 25,596 = 7.1\%$ lower than the corresponding cost with the policy that minimizes long-run average annual costs per person. We also see that the optimal long-run average annual costs per person are $(762.7 - 645.4)/645.4 = 18.2\%$ lower than the long-run average annual costs per person of the policy that optimizes discounted costs.

**Policy point:** Table 2 indicates that the three policies from Table 1 that invest significantly in general awareness each have far fewer undiagnosed individuals than the other policies. These three policies also lead to lower fractions of individuals with early and late stage diabetes and a higher fraction of individuals in healthy (especially to low risk) and IGT (prediabetes) states. Moreover, long-run average QALY measures and population growth rates are higher with these policies.

### 4.2. Do open vs. closed population models and discounted vs. long-run average goals matter?

Figure 4 plots the performance of different 5000 randomly chosen fixed policies with respect to the discounted open population cost ($J_{5,\infty}$) and closed population cost ($\tilde{J}_{5,\infty}$) per person at time 0. The strong
correlation that is anticipated between these two objective functions is consistent with the clustering of the points along a diagonal. The lower left end of that cluster terminates in a point, which indicates that the optimal policy for these two objective functions is the same in this example. For the discounted WTP objective functions \((J_{\lambda, \infty} \text{ and } \tilde{J}_{\lambda, \infty})\), we also observed that policies that work well for the open population model also work well for the closed population model.

Figure 5 shows that the correlation between the performance of policies for the discounted \((J_{S, \infty})\) and the long-run \((V_{S, \infty})\) cost objectives is much smaller than the correlation observed in Figure 4: points in Figure 5 do not cluster on the diagonal, and policies that optimize \(J_{S, \infty}\) and \(V_{S, \infty}\) are very different. Some insights about the sensitivity of outcomes to policy choices can be gained by viewing the intervention intensity and the associated financial and health outcomes of the four points labeled in Figure 5 and as summarized in Table 3. Point 4 almost optimizes \(J_{S, \infty}\), and its intervention intensity and outcomes closely resemble those for \(z^{J_{S, \infty}}\) in Table 1 and Table 2.

Point 2 almost optimizes \(V_{S, \infty}\) but point 2 has somewhat less general awareness (3.737 not 4.185) and more late stage intervention (0.965 not 0.003) than does \(z^{V_{S, \infty}}\). Thus, it appears that the policies that are optimal for long-run average costs are not sensitive to the degree of late stage intervention. This hypothesis is validated by the intervention values of point 1. Point 1 suggests almost 10 interventions per late stage case, with little degradation in performance on long-run average costs but a significant increase in infinite horizon discounted costs.

Outcomes for point 3 suggest that reducing general awareness by 50% or more, as compared to what is optimal for \(V_{S, \infty}\), can degrade the long-run average costs, even if it does not degrade infinite horizon NPV.

We observed similar characteristics in the comparison of \(J_{S, \infty}\) versus \(\tilde{V}_{S, \infty}\), as we observed above for the comparison of \(J_{S, \infty}\) versus \(V_{S, \infty}\).
Table 3  Some Policies Plotted in Figure 5 and Associated Outcomes.

<table>
<thead>
<tr>
<th>z1</th>
<th>Point 1</th>
<th>Point 2</th>
<th>Point 3</th>
<th>Point 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.963</td>
<td>3.737</td>
<td>1.74</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>z2</td>
<td>1.459</td>
<td>1.556</td>
<td>1.355</td>
<td>1.384</td>
</tr>
<tr>
<td>z3</td>
<td>1.450</td>
<td>1.178</td>
<td>1.667</td>
<td>1.2398</td>
</tr>
<tr>
<td>z4</td>
<td>9.824</td>
<td>0.965</td>
<td>0.208</td>
<td>0.2761</td>
</tr>
<tr>
<td>J_{S,\infty}</td>
<td>28550</td>
<td>27370</td>
<td>27220</td>
<td>25596</td>
</tr>
<tr>
<td>V_{S,\infty}</td>
<td>650.6</td>
<td>648</td>
<td>690.3</td>
<td>762.7</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.8134</td>
<td>6.8157</td>
<td>6.8351</td>
<td>7.0446</td>
</tr>
<tr>
<td>QALY</td>
<td>0.9856</td>
<td>0.9841</td>
<td>0.9720</td>
<td>0.9525</td>
</tr>
<tr>
<td>Growth Rate</td>
<td>1.6079%</td>
<td>1.5874%</td>
<td>1.5396%</td>
<td>1.3746%</td>
</tr>
</tbody>
</table>

Policy point: The choice of (short-term focused) discounted versus long-run average goals can lead to vastly different policies for optimal portfolios of interventions. Two policies that perform well with respect to one objective might perform very differently on another objective.

Policy point: Optimal long-run average cost objectives are strongly supported by general awareness for healthy lifestyles, screening opportunities and coaching for people with IGT and early stage diabetes, but are less sensitive to the degree of interventions for people with late stage diabetes.

4.3. What predicted benefits are there from immediate diagnosis of IGT and T2DM?

The model in this paper assumes that we know the number of individuals in each compartment (e.g., whether a given individual is diagnosed and has IGT, or early or late stage diabetes). This is done to see how policies are influenced in the presence of full information. The approximation might be relatively reasonable following the Weqaya program in Abu Dhabi which required all nationals to be screened [Hajat et al. 2012]. In other communities the assumption may be less valid.

We can get some intuition for how valuable such information might be by comparing our model above with a slightly modified model that assumes a costless and 100% immediate diagnosis rate. This can be implemented by forcing individuals in the compartments for undiagnosed IGT, early and late stage to flow to diagnosed compartments in one time step. Table 4 gives the optimal fixed policies under different objective functions with immediate diagnosis and Table 5 presents the corresponding objective values and demographic outcomes. Differences in optimal policies are observed for the purely financial objectives. We first examine the discounted cost formulation $J_{S,\infty}$. The optimal policy $z^{*}_{S,\infty}$ for $J_{S,\infty}$ requires more frequent intervention for those with IGT and early stage T2DM, and somewhat less frequent interventions for late stage T2DM. These differences do not seem to be large from a practical perspective. The NPV per person for $z^{*}_{S,\infty}$ with immediate diagnosis, US$26 263, is higher than without immediate diagnosis (US$25 596 from Table 2). This is because more diagnosed individuals implies more treatment and intervention costs.
Table 4  Optimal Fixed Policies with Immediate Diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>$z^*_{J_s,00}$</th>
<th>$z^*_{J_v,00}$</th>
<th>$z^*_{V_s,00}$</th>
<th>$z^*_{V_v,00}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Awareness Coverage</td>
<td>0.0000</td>
<td>21.2241</td>
<td>0.0000</td>
<td>13.8573</td>
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<tr>
<td>IGT Coaching</td>
<td>1.4219</td>
<td>2.5894</td>
<td>1.6219</td>
<td>2.5302</td>
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<tr>
<td>Early Stage Coaching</td>
<td>1.2932</td>
<td>2.6265</td>
<td>1.4478</td>
<td>0.0000</td>
</tr>
<tr>
<td>Late Stage Coaching</td>
<td>0.2328</td>
<td>2.4191</td>
<td>0.0003</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Table 5  Demographic Outcomes Under Fixed Policies and Immediate Diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>$z = 0$</th>
<th>$z^{\text{base}}$</th>
<th>$z^*_{J_s,00}$</th>
<th>$z^*_{J_v,00}$</th>
<th>$z^*_{V_s,00}$</th>
<th>$z^*_{V_v,00}$</th>
</tr>
</thead>
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<tr>
<td>$J_{S,00}$</td>
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<td>27795</td>
<td>26263</td>
<td>32988</td>
<td>26286</td>
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<td>-1243200</td>
<td>-1262200</td>
<td>-1297600</td>
<td>-1358100</td>
<td>-1296900</td>
<td>-1331100</td>
</tr>
<tr>
<td>$V_{S,00}$</td>
<td>870.7357</td>
<td>795.1785</td>
<td>618.2622</td>
<td>811.915</td>
<td>616.4690</td>
<td>740.8348</td>
</tr>
<tr>
<td>$V_{L,00}$</td>
<td>-46777</td>
<td>-47211</td>
<td>-48551</td>
<td>-48787</td>
<td>-48599</td>
<td>-48852</td>
</tr>
<tr>
<td>Low Risk</td>
<td>0.2893</td>
<td>0.2958</td>
<td>0.2824</td>
<td>0.7395</td>
<td>0.2824</td>
<td>0.6875</td>
</tr>
<tr>
<td>High Risk</td>
<td>0.2640</td>
<td>0.2564</td>
<td>0.2578</td>
<td>0.0055</td>
<td>0.2577</td>
<td>0.0371</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>0.0130</td>
<td>0.0127</td>
<td>0.0127</td>
<td>0.0075</td>
<td>0.0127</td>
<td>0.0082</td>
</tr>
<tr>
<td>IGT</td>
<td>0.2414</td>
<td>0.2684</td>
<td>0.3741</td>
<td>0.2120</td>
<td>0.3782</td>
<td>0.2339</td>
</tr>
<tr>
<td>Early</td>
<td>0.1641</td>
<td>0.1468</td>
<td>0.0704</td>
<td>0.0344</td>
<td>0.0669</td>
<td>0.0290</td>
</tr>
<tr>
<td>Late</td>
<td>0.0282</td>
<td>0.0199</td>
<td>0.0026</td>
<td>0.0010</td>
<td>0.0022</td>
<td>0.0044</td>
</tr>
<tr>
<td>QALY</td>
<td>0.9530</td>
<td>0.9601</td>
<td>0.9834</td>
<td>0.9920</td>
<td>0.9843</td>
<td>0.9919</td>
</tr>
<tr>
<td>Growth Rate</td>
<td>1.3838%</td>
<td>1.4442%</td>
<td>1.5425%</td>
<td>1.7419%</td>
<td>1.5448%</td>
<td>1.7011%</td>
</tr>
</tbody>
</table>

A greater practical difference is observed for the long-run average cost, $V_{S,00}$. While general awareness is an active part of the optimal portfolio when there is no immediate diagnosis, it is not an active part of the optimal portfolio when there is immediate diagnosis ($z^*_{V_s,00}$ in row for general awareness is 0). Thus, the benefit of general awareness for optimizing $V_{S,00}$ seems to be in its role in identifying undetected cases more than in keeping healthy people to become or to remain at low risk. The reduction in general awareness intervention results in a lower per person cost ($616 instead of $645/person/year) if immediate diagnosis were costless, but individuals would be higher risk of IGT, and IGT prevalence would be higher.

The optimal policies for the two WTP objectives, $(z^*_{J_s,00}$ and $z^*_{V_s,00})$, are almost identical whether immediate diagnosis is available or not. Thus, a WTP decision maker’s optimal policies do not strongly depend on immediate diagnosis – the high rates of general awareness associated with those policies (as expected from the monetizing of health) are sufficient for detecting new cases.

Policy point: For WTP goals, the main benefit of general awareness interventions is in keeping healthy people healthy. For financial goals, the benefit of general awareness appears to be its role in screening.
4.4. How do the optimal policies affect population growth rates?

Population growth rates are a function of per capita birth rates and death rates. Birth and death rates are (crudely) represented here by assuming birth rates are constant through time; that more births per capita occur with an increased lifespan; and that risk factors from T2DM, its complications, and clinical indicators may influence death rates.

We get an idea of how policies influence birth rates by assessing how costs and QALYs both vary as implicit functions of the WTP parameter $\lambda$. As $\lambda$ varies, so does the optimal $z^{J,\infty}$ for the discounted WTP objective. Figure 6 displays the infinite horizon discounted QALYs (per person at time 0) $JQALY,\infty(z^{J,\infty},J\lambda,\infty)$ and the long-run population growth rate $r_{0,z^{J,\infty}}$ for values of $\lambda = 0, 1K, 2K, \ldots, 100K$ US$/QALY. With increasing values of $\lambda$, a higher fraction of people stay in compartments representing better health. This in turn results in more people with a lower risk of death, and thereby a greater population growth rate.

Figure 7 plots long-run average (not discounted) QALYs on the horizontal axis. Figure 7 is qualitatively different from Figure 6 in that its curve is not a smoothly increasing function of $\lambda$ (points correspond to different $z^{V,\infty}$). Average QALYs indeed are increasing in $\lambda$ in this plot, but there is a small local maximum in the growth rate in the curved left-hand portion of the curve. This local maximum occurs when $\lambda \approx 25K$ US$/QALY. In the curved portion of the graph, $z^{J,\infty}$ has nonzero levels of general awareness, IGT coaching and early stage coaching (no late stage coaching). For $\lambda \geq 27K$ US$/QALY, only general awareness and IGT coaching are included in the optimal portfolio and general awareness is high $z_{1}^{J,\infty} > 10$. Increases in $\lambda$ lead to an almost linear relationship between $VQALY,\infty(z^{J,\infty})$ and $(r_{0,z^{J,\infty}})$ (right hand portion of Figure 7), with increases in $\lambda$ leading to decreasing marginal returns in those two objectives.
4.5. Which flow rate parameters of this model influence infinite horizon discounted NPV?

This study used point estimators for all parameters. A full uncertainty analysis is beyond the scope of this paper. We did examine, however, which parameters seem to most strongly influence the predicted infinite horizon discounted NPV of the optimal policy in order to get a sense of which parameters seem to most strongly influence financial outcomes. To do this, we modified the point estimates of a broad variety of transition parameters (over 30 of them) by 5% of their original values. After varying each parameter individually, we recomputed its associated optimal policy for \( J_{S,\infty} \).

In summary, most parameters resulted in only a small change in \( J_{S,\infty} \) (a difference of less than ±0.03%). There were only a few parameters with greater effects. A 5% change in the rate of progression from early stage to late stage diabetes resulted in a 0.46% change in \( J_{S,\infty} \). A 5% change in the rate of progression from IGT to early stage diabetes resulted in a 0.23% change in \( J_{S,\infty} \). A 5% change in the rate of progression from healthy to undiagnosed IGT resulted in a 0.13% change in \( J_{S,\infty} \).

Policy point: The parameters that most greatly influence \( J_{S,\infty} \) are the disease progression parameters (relative to other parameters such as those that describe how interventions influence disease management and reduce HbA1c). This suggests that better information about these parameters should be prioritized above others if the goal is to better manage the infinite horizon cost burden of T2DM in this modeled population.

4.6. Which interventions should be funded more if the budget were increased?

Implementing the optimal budget might be difficult to do in the short term due to constraints on capacity. An interesting question is how to allocate an extra \( X\% \) of funds beyond current levels of activity, \( z_{base} \). Here, we consider how a policy maker should allocate an additional intervention budget for one year at the start of an infinite planning horizon. For illustration, we assume that the level of interventions returns to \( z_{base} \) in subsequent time periods. More specifically, Table 6 gives the incremental number of interventions in the first year, beyond base levels, of the four interventions, if the \( J_{\lambda,\infty}(z_{t}) \) objective function were minimized over the class of policies such that \( z_{0} \geq z_{base} \) and \( z_{t} = z_{base} \) for \( t = 1, 2, \ldots \). The tested budget increments represent increases of 1%, 5%, 10% and 20% of the total annual costs (of disease management, complications, and a base level of interventions).

Policy point: Assuming that a decision maker values health at \( \lambda = 50 \text{ US$/QALY} \), temporary budget increases of up to 5% should be focused on general awareness to improve healthy lifestyles and encourage screening in this modeled context. Beyond 5%, coaching for IGT should also increase. These increments in budget actually decrease the overall WTP measure (the values of \( J_{S,\infty} \) in the table are below the value US$ \(-1.241 \times 10^6 \) of \( J_{S,\infty}(z_{base}) \) from Table 2), so the associated incremental interventions are cost effective.

A similar experiment (data not shown) for the \( J_{\lambda,\infty}(z_{t}) \) objective function suggests that a decision maker that uses an NPV rather than WTP formulation should allocate a budget increase (up to 5%) to IGT coaching. With a 10% increase, early stage coaching should also receive an increment. These increases in disease management would be cost saving (treatment cost savings would outweigh the added intervention costs).
Table 6  
Optimal Level of Additional Interventions over Base Level with $J_{λ,∞}$ objective.

<table>
<thead>
<tr>
<th>Extra Budget</th>
<th>$z_1$</th>
<th>$z_2$</th>
<th>$z_3$</th>
<th>$z_4$</th>
<th>$J_{λ,∞}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% (11.7 $)</td>
<td>0.7797</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>$-1.2443 \times 10^6$</td>
</tr>
<tr>
<td>5% (58.38 $)</td>
<td>3.8920</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>$-1.2580 \times 10^6$</td>
</tr>
<tr>
<td>10% (116.95 $)</td>
<td>5.6684</td>
<td>0.6385</td>
<td>0.0000</td>
<td>0.0000</td>
<td>$-1.2591 \times 10^6$</td>
</tr>
<tr>
<td>20% (233.92 $)</td>
<td>9.1796</td>
<td>1.9245</td>
<td>0.0000</td>
<td>0.0000</td>
<td>$-1.2602 \times 10^6$</td>
</tr>
</tbody>
</table>

5. Stationary policies

The static policies explored above require that the same number of interventions per person are applied, independent of the number of people in each disease state, in the sense that $z_t = z$ can not vary through time. One might be able to obtain better results by allowing $z_t$ to depend on $x_t$. Such policies may be difficult to implement: tracking $x_t$ through time is more challenging than only estimating $x_t$ (for optimal policies for discounted objectives) or not estimating $x_t$ at all (for optimal long-run average objectives). Moreover, changing the level of interventions from year to year may raise equity issues.

This section shows that there is an optimal policy for the infinite horizon costs $J_{S,∞}$ that is stationary (does not depend on $t$ but may depend on $x_t$). We also explore several heuristics to assess the net potential benefit associated with a stationary policy, assuming one could be adopted.

Structural results. The cost per stage in (3) is positive and unbounded given that the population vector is not bounded. The Positivity Property defined in Bertsekas (2007, chap. 3) thus applies to (3). Hence, the results of Theorem 3.1.7 as outlined in Bertsekas (2007) chap. 3) are applicable to prove the existence of a stationary optimal policy minimizing the cost function (3).

To assure the existence of such a stationary policy, one needs the existence of at least one policy which results in a finite objective function. One sufficient condition for is the following assumption that there exists a fixed policy that results in a finite objective function and that does not result in the population size shrinking to 0. The assumption is valid in our application, as can be verified by the data fitting process of §8 and the lemma that follows.

Assumption 2. The set $S_3$ of sustainable fixed policies is non-empty.

Lemma 4. If $\max_i 1 - d_i + \sum_{j=1}^{N_c} b_{i,j} < 1/\beta$ then Assumption 2 is satisfied.

We also use a technical condition regarding the marginal cost of interventions and transition rates.

Assumption 3. Both $C(z)$ and $P(z)$ are continuous in $z$.

Proposition 1. If Assumptions 2 and 3 hold, then there exists a stationary policy that is optimal for minimizing $J_{S,∞}$ in (3).

The analysis is easily extended to prove the existence of a stationary policy that is optimal for the infinite horizon discounted total QALYs, $J_{QALY,∞}$. 
The optimal stationary policy, $z^*(x)$ may be challenging to compute, given that the decision vector is 4 dimensional and the state vector is high dimensional. We therefore explore several heuristic policies.

**Heuristic A** repeatedly applies the infinite horizon cost minimization over fixed policies at each time period $t$. More specifically, the policy maker starts from new at each period $t$, and finds a new set of fixed polices to minimize $J_{\infty,\infty}$ starting from time $t$ with $x_t$, which is the same as choosing $z_t$ to minimize $H^A_t = (c' + C(z_t)B)(I - \beta P(z_t))^{-1}x_t$ for each $t$.

**Heuristic B** uses approximate dynamic programming with the synchronous fitted value iteration algorithm of Kveton et al. (2006) to obtain a stationary policy. We used $N_c + 1$ basis functions (the constant function plus one linear basis function per compartment) to (approximately) minimize $J_{\infty,\infty}$. Specifically, $z_t$ minimizes $H^B_t = (c + C(z_t))x_t + \beta \phi[1 \ 0; 0 \ P(z_t)][1; x_t]$ for each $t$, where $\phi$ is a vector of coefficients for the linear basis functions (estimated with least squares); $[1 \ 0; 0 \ P(z_t)]$ and $[1; x_t]$ represent augmentations of the state to allow for the linear term; so that $\phi[1 \ 0; 0 \ P(z_t)][1; x_t]$ is an affine approximation to the value function at the subsequent time step.

**Heuristic C** is motivated by the case of a policy maker who minimizes the sum of costs due to T2DM treatment and intervention in period $t$, plus future infinite horizon discounted costs starting from $t+1$ with $x_{t+1}$, assuming no further interventions were possible. Formally, $z_t$ is chosen at time $t$ to minimize $H^C_t = (c' + C(z_t)B)x_t + (c' + C(0)B)(I - \beta P(0))^{-1}P(z_t)x_t$.

**Heuristic D** considers the case of a myopic policy maker who, at each time period, minimizes the cost of interventions plus cost of chronic care at the end of the following period: $H^D_t = (c' + C(z_t)B)x_t + c'\beta P(z_t)x_t$.

Theoretically, the optimal stationary policy will perform at least as well as the optimal fixed policy, because fixed policies are special cases of stationary policies. A heuristic may be suboptimal relative to the optimal stationary policy. We tested whether the heuristic stationary policy can improve upon the optimal fixed policy (recall that $J_{\infty,\infty}(z^*_{\infty,\infty}) = $25 596 per person). Heuristic A improved upon this only slightly, with $J_{\infty,\infty}$(Heuristic A) = $25 594. Heuristic B, the ADP solution, showed a somewhat better improvement, with $J_{\infty,\infty}$(Heuristic B) = $24 281 (5% cost improvement). It is worth noting that the choice to implement this dynamic heuristic should depend on whether the added cost of the needed information collection (as compared with the reduced informational needs for the optimal fixed policy), is more or less than the anticipated 5% cost savings. Heuristics C and D were not effective and resulted in 0.1% and 0.23% cost increases, respectively.

*Policy point:* The ADP solution is the best of these heuristics. The ADP solution achieved its gains, as compared to the optimal fixed policy, by increasing intervention intensity when there were a higher fraction of individuals in compartments associated with higher HbA$_{1c}$ levels and treatment costs.

6. Conclusions

A compartmental model that incorporates the interaction of disease interventions and long-run population dynamics can be useful for several reasons. It allows for the exploration of non-additive costs and benefits.
that are obtained from the interaction of interventions, as well as an understanding of differences between cost effectiveness in the short-term and those in the long-term. For example, in our application of these concepts to the T2DM challenge in the GCC states, general awareness is not found to be cost saving from a classical NPV perspective but is cost saving from a long-term average cost perspective. Sequentially optimizing interventions intensities separately may result in a suboptimal performance as compared to a holistic joint optimization of a portfolio of interventions. These observations and the other policy points in the numerical section may differ in other populations and should be taken with an understanding of the strengths and caveats associated with the data fitting process. That said, the portfolio optimization approach proposed here appears to be an interesting direction for further work on mathematical modeling for sustainable, systems-oriented health policy design.

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References


7. Proofs of Mathematical Claims

*Proof of Lemma 4* All of the elements of $P = P(z)$ are non-negative because $P$ is a sum of products of non-negative square matrices. For a proof by contradiction, suppose that $P$ is reducible. By the definition of reducibility, there is a permutation $\pi$ with a corresponding permutation matrix $[\pi]$ such that $\bar{P} = [\pi]P[\pi] = \left[\begin{array}{cc} P_1 & P_2 \\ 0 & P_3 \end{array}\right]$, where $P_1$ is a $k \times k$ square matrix and $P_3$ is a $(N_C - k) \times (N_C - k)$ square matrix, for some $1 \leq k < N_C$.

Then, $\bar{P}_{m,n} = 0$ for $m = k + 1, \ldots, N_C$, $n = 1, \ldots, k$. Therefore, for $I = \{\pi^{-1}(1), \ldots, \pi^{-1}(k)\}$, there exists a non-empty set of indices $I^c = \{\pi^{-1}(k + 1), \ldots, \pi^{-1}(N_C)\}$ such that $P_{I^c,I} = 0$.

Let $i$ the compartment in Assumption [1](i) into which births occur. Then $i$ is either in $I$ or $I^c$.

If $i \in I$ then $P_{i,j} = 0$ for all $j \in I$. By Assumption [1](i) and (ii), $B_{i,j} > 0$, for all $j$ and $F_{i,j} > 0$. Because $P_{i,j} \geq F_{i,j}B_{i,j}$, we conclude that $P_{i,j} > 0$ and therefore that $i \notin I^c$ (which contradicts $i \in I^c$).

If $i \in I$ then $P_{j,i} = 0$ for all $j \in I$. By Assumption [1](iii), all compartments $j \in \{1, \ldots, N_C\}$ are reachable from $i$ using arcs with positive flows, meaning that there is a $k > 0$ such that $\bar{P}_{k(i)} = 0$ for all $k$ by the reducibility assumption. This contradiction implies that $P$ is irreducible.

Furthermore, for this $i$, $P_{i,j} = \sum_{j=1}^{N_C} F_{i,j}B_{j,i}$, where $F_{i,j}, B_{j,i} \geq 0$ for all $j$. By Assumption [1](i) and (ii), we have $F_{i,j} > 0$ and $B_{i,j} > 0$, so that $B_{i,i} = 1 - d_i + b_i > 0$ (because $d_i \leq 1$). Then, $P_{i,j} > 0$, indicating that at least one of the diagonal elements of $P$ is positive. Therefore, $P$ is a primitive matrix since it is both irreducible and has at least one non-zero diagonal element. $\Box$
Proof of Lemma 2. Claims (i) and (iii) follow directly from Assumption 1, Lemma 1, the Perron-Frobenius theorem (parts 1–4) and the comment following the statement of the theorem that applies because \( P(z) \) is non-negative and primitive. The notation \( r_{0,x} \) and \( \nu_{0,x} \) in the claim emphasizes a dependence on \( z \).

(ii) Consider a spectral decomposition \( P = \Phi \Sigma \Phi^{-1} \), where \( \Lambda = \text{diag}[r_0 r_1 \ldots r_{N-1}] \) is a matrix of eigenvalues on the diagonal and 0 elsewhere such that \( |r_0| > |r_i| \) for each \( i \); and where \( \Phi \) is a matrix of right generalized eigenvectors in its columns, \( V = [\nu_0 \nu_1 \ldots \nu_{N-1}] \), so that the generalized eigenvectors span \( N_c \).

(Here, \( r_0 = r_{0,x} \) and \( \nu_0 = \nu_{0,x} \).)

We can therefore write \( x_t \) as a linear combination of right generalized eigenvectors of \( P \), so there is a \( \tilde{\alpha} = [\alpha_0 \alpha_1 \ldots \alpha_{N-1}] \) with \( x_t = V \tilde{\alpha} \). Thus \( x_t = \Phi x_0 = \Phi A V^{-1} V \tilde{\alpha} = \Phi \Lambda \tilde{\alpha} \) and

\[
\frac{\|x_{t+1}\|_1}{\|x_t\|_1} = \frac{\|\Phi x_0\|_1}{\|\Phi x_0\|_1} = \frac{\|\Phi A \tilde{\alpha}\|_1}{\|\Phi \Lambda \tilde{\alpha}\|_1} = \frac{\|\nu_0 r_0^+ \alpha_0 + \nu_1 r_1^+ \alpha_1 + \ldots + \nu_{N-1} r_{N-1}^+ \alpha_{N-1}\|_1}{\|\nu_0 \Lambda \tilde{\alpha}\|_1} = \frac{\|\nu_0 r_0^+ \alpha_0 + \nu_1 r_1^+ \alpha_1 + \ldots + \nu_{N-1} r_{N-1}^+ \alpha_{N-1}\|_1}{\|\nu_0 \Lambda \tilde{\alpha}\|_1} = \frac{\|\nu_0 \alpha_0 + f_1(t)\|_1}{\|\nu_0 \alpha_0 + f_1(t)\|_1},
\]

where the numerator and denominators in the last equality define \( f_1 \) and \( f_2 \), respectively. The unique dominance of \( r_0 \) given by the Perron-Frobenius theorem implies \( \lim_{t \to \infty} f_1(t) = 0 \) for \( i = 1, 2 \). We conclude that

\( \lim_{t \to \infty} \frac{\|x_{t+1}\|_1}{\|x_t\|_1} = r_0 = r_{0,x} \), so that \( r_0 = r_{0,x} \) is justifiably the long-run population growth rate.

(iv) The fraction of individuals in each compartment at time \( t \) is

\[
\frac{x_t}{\|x_t\|_1} = \frac{r_0 \nu_0 \alpha_0 + r_1 \nu_1 \alpha_1 + \ldots + \nu_{N-1} \alpha_{N-1}}{\|x_0\|_1} = \frac{\nu_0 \alpha_0 + f_1(t)}{\|\nu_0 \alpha_0 + f_1(t)\|_1},
\]

We conclude that \( \lim_{t \to \infty} x_t/\|x_t\|_1 = \nu_0/\|\nu_0\|_1 \), where \( \nu_0 = \nu_{0,x} \) as claimed. □

Proof of Lemma 3. By Lemma 3 the limit that defines \( J_{\Delta}(z) \) converges if \( r_{0,x} < 1/\beta \).

Note that the \( i \)th row of the birth and death matrix \( B \) sums to \( \zeta_i = 1 - d_i + \sum_{j=1}^{N_c} b_{i,j} \). (Our model assumed that interventions do not directly change birth or death rates for a given compartment – interventions can indirectly change those rates by changing flows between compartments with potentially different rates.) As \( B \) is nonnegative, its dominant eigenvalue \( \zeta_0 \) satisfies \( \min \zeta_i \leq \zeta_0 \leq \max \zeta_i \) (Luenberger 1979, p. 194).

Note that \( P(z) = F B \) for some probability transition matrix \( F \) that may depend on \( z \). After a little algebra with the infinity norm \( \|A\|_\infty \overset{\Delta}{=} \max_i \sum_j |a_{ij}| \), the observation that \( F \) and \( B \) are nonnegative, and the property of norms \( \|FB\|_\infty \leq \|F\|_\infty \|B\|_\infty \), we find that the dominant eigenvalue \( r_{0,x} \) of \( P(z) \) can be no greater than the product of dominant eigenvalues of \( F \) and \( B \). The eigenvalue of \( F \) with greatest magnitude is \( 1 \) because \( F \) is a probability transition matrix. Thus, \( r_{0,x} \leq \max \zeta_i \). Thus, \( \beta r_{0,x} < 1 \) if \( \max \zeta_i < 1/\beta \), as claimed. □
Proof of Proposition 7. Recall the objective function $J_{S,\infty}(z_s) = \lim_{t \to \infty} \sum_{j=0}^{t-1} \beta^j(c'x_t + C(z_t)Bx_t)$ and dynamic $x_{t+1} = P(z)x_t$. Let $J^* = \inf J_{S,\infty}(z_s)$.

The cost per stage is positive at each step for all spending levels, and it is unbounded above because the $x_t$ is not bounded. Let $J_0$ be the zero function on $R_{\infty}^C$, and let $T$ denote the Bellman optimality operator. The dynamic programming formulation gives

$$J_0(x) = 0$$

$$(T^{k+1}J_0)(x) = \min_{z \in R_{\infty}^N} \{c' + C(z)Bx + \beta T^k J_0(P(z)x)\}$$

By Assumption 3 the preceding equations, and induction, $T^k J_0(x_0)$ is continuous in $z$ for all $k$. By Assumption 2 there is a fixed policy with $z_t = z$ for all $t$ that is sustainable, so that $J_{S,\infty}(z) < \infty$. Thus $J^*$ is finite.

The definition of positivity as used in Proposition 3.1.7 in Bertsekas (2007) p. 144 holds for our problem. Hence, if we can show that the sets $S_k(x, \lambda) = \{z \geq 0 | c'x + C(z)Bx + \beta T^k J_0(P(z)x) \leq \lambda\}$ are compact subsets of a Euclidian space for every $x \in R_{\infty}^C$, $\lambda \in R$ and for all $k$ greater than some integer $k$, we can conclude that $J_{\infty} = T J_{\infty} = J^*$ where $J_{\infty}(x) = \lim_{k \to \infty} T^k J_0(x)$, and that a stationary optimal policy exists.

First, note that $\lim_{z \to \infty} c'x + C(z)Bx + \beta T^k J_0(P(z)x) = \infty$ for $i = 1, 2, 3, 4$. Hence the sets $S_k(x, \lambda)$ are bounded. The sets $S_k(x, \lambda)$ are closed because $c'x + C(z)Bx + \beta T^k J_0(P(z)x)$ is a continuous function of $z$.

Therefore, by Proposition 3.1.7 in Bertsekas (2007): $\lim_{k \to \infty} (T^k J_0)(x) = J^*(x)$. Furthermore, an optimal stationary policy $z^*_k(x_0) = (z^*(x_0), z^*(x_1), \ldots)$ can be obtained by minimizing the right hand side of: $J_{\infty}(x) = (T J_{\infty})(x) = \min_{z} [c'x + C(z)Bx + \beta J_{\infty}(P(z)x)]$. □

8. Further Details about the T2DM Model and Parameter Estimation

The structure of the model in Figure 1 was chosen to comprehend features of disease progression, the effect of interventions on compliance with self-management of T2DM, and their effects on the clinical indicator HbA1c (which is measurable and has been associated with costs and risks of complications due to T2DM). Some limitations of this model are mentioned at the end of this section.

The parameter estimation of the model for the numerical experiments in the paper was done to reflect the adult population of Abu Dhabi nationals to the greatest extent possible. This proceeded in several phases. We first estimated the initial population distribution $x_0$ as well as birth and death rates to match the population distribution as partly revealed by Weqaya program which screened all nationals at the time of a health insurance reform. Here, “birth” means being included in the population with a health insurance card at age 18. We then estimated the annual cost of disease management from data from the UAE and/or the GCC. QALY scores required resorting to data sources from outside of the GCC.

The fitting of parameters for the flow rates as a function of the intervention intensities was more challenging: the system is rapidly changing (no stable steady state) and a full set of data is not available; there is
data for some but not all flow rates; and combining parameter estimates from different sources runs the risk of having individually justifiable parameters that lead to inconsistent representations of a single system.

In summary, we estimated flow rate parameters by first establishing relationships between as many flows as possible using relative risk factors. The remaining parameters were fitted through minimizing a complicated objective function whose terms involved: (i) relative squared-error discrepancy between the fraction of individuals in each compartment, $x_0/\|x_0\|_1$, at time 0 and the stationary distribution $\nu_{0,base}$ that results from employing a fixed base portfolio of interventions $z_{base}$, to fit parameters when base level interventions were active, (ii) squared-error discrepancy between the average HbA$_1c$ of individuals with diagnosed T2DM when targeted interventions were raised by one (to $z_{base}+[0,1,1,1]'$) as predicted by the model compared with the values reported in the literature, and (iii) squared-error discrepancy of the effect of general awareness campaigns on the fraction of healthy people with low risk and the fraction of undiagnosed that are detected per time period, as predicted by the model as compared with risk reduction and detection measured in empirical studies. For (i) above, compartments with undiagnosed conditions were aggregated in the least-squares term because the particular disease state of an undiagnosed case is unknown.

A more detailed description of this parameter estimation process is as follows. As part of the process, we assumed that the effect of interventions on the flow rates $f_{i,j}$ were logistic functions. We set $z_{base} = [.3 .3 .3 .3]'$. This process resulted in the flow rates in Figure 8.
Initial population distribution, $x_0$. Table 7 summarizes the sources used to estimate the proportion of individuals in each compartment at the moments prior to the recent massive screening in Abu Dhabi. While diabetes prevalence may be somewhat higher in Abu Dhabi as compared to other Emirates or GCC countries, those other regions have not yet had a full screening. The fitting process may therefore also be relevant for those other regions.

The Weqaya Screening of the Health Authority-Abu Dhabi (HAAD) was an important information source. Weqaya started in April 2008 aiming to respond to the increase in cardio-vascular problems in Abu Dhabi’s Emirati population, to date 96% of that population of 180 000 adults (18 years an over) has been screened for risk factors related to cardio-vascular problems including diabetes and obesity. The International Diabetes Federation (IDF) estimated that the undiagnosed diabetics constitute 62% of all cases [IDF 2006], and that half of the diagnosed diabetic population is in the late stage of diabetes having developed complications. To the best of our knowledge, the proportion of the undiagnosed population in early and late stage is not identified in prior studies. Hence, the proportion of the undiagnosed population in the late stage versus early stage is fit by the least-squares error minimization.

We used a conservative estimate for the proportion of healthy high risk (here, overweight to simplify): we assumed that all diabetics and pre-diabetics were overweight so that the proportion of people at high risk of developing pre-diabetes is given by $70% - 44% = 26%$. The compliance rate (under the base rate of intervention) of 40% among people with diabetes was based on a study of dietary habits in Saudi Arabia. We assume that the overall compliance rate including the drug refill and doctor visit rates is the same with the above percentage and is comparable between early and late stage diabetics. [Harris et al. 1999] gives the respective proportions of each glycemic control group both for diabetics under insulin and diet alone. We assume that insulin treatment is administered to those who do not comply to dietary modifications, and the patients treated with diet alone are considered to be compliant. [Harris et al. 1999] also indicates that the average HbA1c for the highest HbA1c group (where HbA1c > 8%), is different in compliant and non-compliant compartments. Given these, we can work out the HbA1c distribution for compliant and non-compliant diabetics. These proportions are assumed to be the same for IGT, early and late stages.

The assumptions above result in the fraction of people in each compartment that is given in Figure 1.

Birth and death rates. The Statistics Centre-Abu Dhabi reports 2.11 deaths per 1000 people years for Emirati nationals [SCAD 2011]. Death rates $d_i$ for each compartment were then determined by the relative risk for death by disease state, the overall death rate, and the population distribution determined above. This gives $d = [1.9 1.5 2.1 2.1 2.1 2.1 2.1 2.1 3.3 4.1 3.3 3.3 2.7 4.1 3.3 2.7 3.9 4.9 3.9 3.9 3.2 4.9 3.9 3.2 4.9 3.9 3.2] \times 10^{-3}$.

The average birth rate for Abu Dhabi nationals is $b = 0.0311$ [SCAD 2011]. Because the modeled population is adults at age 18, is possible for "births" (arrivals to the model) come not only to healthy compartments, but also to compartments with T2DM. To models an association in T2DM outcomes within families,
Table 7  Parameters For Estimating the Diabetic Population Distribution in the UAE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction diabetic</td>
<td>21%</td>
<td>HAAD (2011)</td>
</tr>
<tr>
<td>Fraction pre-diabetes + diabetics</td>
<td>44%</td>
<td>Khoja et al. (2010)</td>
</tr>
<tr>
<td>Fraction pre-diabetic</td>
<td>23%</td>
<td>computed (44% - 21%)</td>
</tr>
<tr>
<td>Fraction undiagnosed pre-Weqaya</td>
<td>62%</td>
<td>Lasry and Silva (2010)</td>
</tr>
<tr>
<td>Fraction overweight</td>
<td>70%</td>
<td>HAAD (2011)</td>
</tr>
<tr>
<td>Fraction healthy high risk</td>
<td>26%</td>
<td>computed (70% - 23% - 21%)</td>
</tr>
<tr>
<td>Fraction healthy low risk</td>
<td>30%</td>
<td>computed (56% - 26%)</td>
</tr>
<tr>
<td>Ratio of early/late stage</td>
<td>1</td>
<td>Lasry and Silva (2010)</td>
</tr>
<tr>
<td>Fraction late stage diabetics</td>
<td>10.5%</td>
<td>computed (21%/2)</td>
</tr>
<tr>
<td>Fraction early stage diabetics</td>
<td>10.5%</td>
<td>computed (21%/2)</td>
</tr>
<tr>
<td>Fract. compliant (good, fair, poor) glycemic control</td>
<td>(73.2%, 11.9%, 14.9%)</td>
<td>Harris et al. (1999)</td>
</tr>
<tr>
<td>Fract. non-compliant with (good, fair, poor) glycemic control</td>
<td>(26.5%, 22.1%, 51.4%)</td>
<td>Harris et al. (1999)</td>
</tr>
<tr>
<td>Compliance rate</td>
<td>40%</td>
<td>Khattab et al. (1999)</td>
</tr>
</tbody>
</table>

Table 8  Parameters for Estimating the Death and Birth Rates in the UAE for Various Stages of Diabetes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death Rate for nationals in Abu Dhabi</td>
<td>2.11/1000 py</td>
<td>SCAD (2011)</td>
</tr>
<tr>
<td>Increase in death rate in higher risk healthy group</td>
<td>0.44</td>
<td>Gonzalez and Hartge (2010)</td>
</tr>
<tr>
<td>Increase in death rate with IGT</td>
<td>0.42</td>
<td>Saydah et al. (1992)</td>
</tr>
<tr>
<td>Increase in death rate with diagnosed diabetes</td>
<td>1.11</td>
<td>Saydah et al. (1992)</td>
</tr>
<tr>
<td>Increase in death rate with undiagnosed diabetes</td>
<td>0.77</td>
<td>Saydah et al. (1992)</td>
</tr>
<tr>
<td>Increase in death rate with late stage diabetes over early stage</td>
<td>0.192</td>
<td>Saydah et al. (1992)</td>
</tr>
<tr>
<td>Increase in death rate per 1% increase in HbA1c for nondiabetic</td>
<td>0.28</td>
<td>Khaw et al. (2001)</td>
</tr>
<tr>
<td>Increase in death rate per 1% increase in HbA1c for diabetic</td>
<td>0.21</td>
<td>Stratton et al. (2000)</td>
</tr>
<tr>
<td>Average Birth Rate for nationals in Abu Dhabi</td>
<td>0.0331</td>
<td>SCAD (2011)</td>
</tr>
</tbody>
</table>

we assumed that individuals in later disease stages are associated with future births that may also be in later stages. Specifically, the nonzero birthrates $b_{i,j}$ to compartment $i$ due to individuals in $j$ were:

$$b_{i,j} = bx_{i,0}/(x_{1,0} + x_{2,0})$$, for $i, j \in \{1, 2\}$

$$b_{i,j} = bx_{i,0}/(x_{1,0} + x_{2,0} + x_{3,0})$$, for $i \in \{1, 2, 3\}$, $j \in \{3, 4, \ldots, 9\}$

$$b_{i,j} = bx_{i,0}/(x_{1,0} + x_{2,0} + x_{3,0} + x_{10,0})$$, for $i \in \{1, 2, 3, 10\}$, $j \in \{10, 11, \ldots, 16\}$

$$b_{i,j} = bx_{i,0}/(x_{1,0} + x_{2,0} + x_{3,0} + x_{10,0} + x_{17,0})$$, for $i \in \{1, 2, 3, 10, 17\}$, $j \in \{17, 18, \ldots, 23\}$

Treatment and intervention costs. Table 9 summarizes data and references that were used to fit the annual treatment costs, $c$. A prime source was Al-Maskari et al. (2010), who studied the average annual costs of treatment for people with diabetes in Al-Ain, a city the Emirate of Abu Dhabi.

The paper indicates that the average medical care cost for people with diabetes without complications is 2005 US $ 1605, and gives the average cost for micro and macro complications. We obtain an estimate of the ratio of prevalences of macro and micro complications with adding up all prevalences of complications in both categories and dividing by the sums. Thus, we establish an estimate of the cost of the first
complication by a weighted sum of the corresponding costs of macro and micro complications. Gilmer et al. (1997) studied the effect of glycemic control on medical costs and estimated that patients with HbA1c levels of 7, 8, 9 and 10% have costs that are 4, 10, 20 and 30% higher than those with an HbA1c of 6%. We assume that the cost increase rates with respect to the HbA1c values are the same for both early and late diabetics. Further more, we assume that the increase in cumulative cost function is pairwise linear. Thus, we can establish the changes in costs for compliant and non-compliant compartments with different HbA1c levels. These data were used to estimate the following annual treatment cost per capita, 

\[ c = [497 497 497 497 497 497 497 497 497 1824 1537 1465 1738 1537 1465 6185 7701 3.6488 6185 7337 6488 6185 7701 3.6488 6185 7337 6488 6185]. \]

including costs not related to diabetes.

General awareness was assumed to cost \( C_1(1) = $15 \) per person per contact. The cost of coaching per person per intervention for people with IGT, Early, and Late Stage diabetes were assumed to cost \( C_2(1) = US$50, C_3(1) = US$81, \) and \( C_4(1) = US$100, \) respectively.

**Health benefits.** We assume that the QALYs per person per year for compartments without diabetes was 1. For the early stage we used a 0.78 QALY per year (Clarke et al. 2002). For late stages, we assumed that a major complication results in a decrease of 0.1285 QALY on average (derived from results in Clarke et al. 2002, with an assumption that each major complication is equally likely), and that a 1 % increase in HbA1c increases the probability of developing complications by 21% (Stratton et al. 2000). Thus we set \( q = [1 1 1 1 1 1 1 1 0.78 0.78 0.78 0.78 0.78 0.78 0.78 0.6515 0.5975 0.6245 0.6515 0.5975 0.6245 0.6515]. \)

**Data and functional form for interventions.** To fit the functional parameters for general awareness, we use the result of Snyder et al. (2004) that suggests that the average increase in healthy behavior is 6% per general awareness contact/message an individual receives. Hence, we assume that the flow from the healthy high-risk compartment to healthy low-risk increases by 6%, and the flow from the healthy low-risk to healthy high-risk decreases by 6% with the first general awareness message over the base level. A general awareness campaign can also motivate people with undiagnosed IGT and early stage diabetes to get diagnosed. This 6% increase in diagnosis rate by the first message/contact is then used in fitting the logistic flow rates \( f_{1,3} = 1/(1 + \exp[-a_{1,1} - a_{1,2}z]) \) and \( f_{11,10} = 1/(1 + \exp[-a_{1,3} - a_{1,4}z]) \). We also assume that the

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**Table 9** Parameters Used in Estimating the Costs for Various Stages of Diabetes (in 2005 US Dollars)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per capita expenditure on health care in Abu Dhabi</td>
<td>US$497</td>
<td>Al-Maskari et al. (2010)</td>
</tr>
<tr>
<td>Annual average cost in early stage diabetes</td>
<td>US$1605</td>
<td>Al-Maskari et al. (2010)</td>
</tr>
<tr>
<td>Average cost of drug therapy</td>
<td>US$2000</td>
<td>Muslim (2010)</td>
</tr>
<tr>
<td>Costs due to microvascular complications</td>
<td>US$3453</td>
<td>Al-Maskari et al. (2010)</td>
</tr>
<tr>
<td>Costs due to macrovascular complications</td>
<td>US$10300</td>
<td>Al-Maskari et al. (2010)</td>
</tr>
<tr>
<td>Ratio of prevalence of macro/micro complications</td>
<td>0.6635</td>
<td>Al-Maskari et al. (2010)</td>
</tr>
<tr>
<td>Weighted annual cost of the first complication</td>
<td>US$6185</td>
<td>Al-Maskari et al. (2010)</td>
</tr>
<tr>
<td>Increased risk of complications per 1% Increase in HbA1c</td>
<td>0.21</td>
<td>Stratton et al. (2000)</td>
</tr>
</tbody>
</table>
Table 10  Parameters used in indirect estimation of vertical flow rates and relative risks of disease progression.

<table>
<thead>
<tr>
<th>Parameter Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average HbA1c in high non-comp</td>
<td>9.7%</td>
<td>Harris et al. (1999)</td>
</tr>
<tr>
<td>Average HbA1c in high comp</td>
<td>9.1%</td>
<td>Harris et al. (1999)</td>
</tr>
<tr>
<td>High and Low Risk population</td>
<td>26%, 30%</td>
<td></td>
</tr>
<tr>
<td>Increase in Risk of comp. 1% HbA1c</td>
<td>21%</td>
<td>Stratton et al. (2000)</td>
</tr>
<tr>
<td>Increase in Risk of comp. non-comp.</td>
<td>31%</td>
<td>Gleason et al. (2011)</td>
</tr>
<tr>
<td>RR with healthy High Risk</td>
<td>4.1((1.64 – 10.22), 95%CI)</td>
<td>Mohan et al. (2008)</td>
</tr>
</tbody>
</table>

Sojourn time for undiagnosed complications was 1 (i.e., a treated complication was assumed to imply a diagnosis during treatment), so the diagnosis rate for late stage diabetics is taken to be $f_{18,17} = 1$. The flow rate from the healthy high-risk to healthy low-risk is taken to have a logistic form: $1/(1 + \exp(-a_{1,5} - a_{1,6}z_1))$. The flow rate from healthy low-risk to healthy high risk is of the form $1 - 1/(1 + \exp(-a_{1,7} - a_{1,8}z_1))$.

To model the effect of coaching on behavior change we use a logistic curve. For $i = 2, 3, 4$ the flow rate from a non-compliant compartment to a compliant compartment is presumed to be of the form $1/(1 + \exp(-a_{i,1} - a_{i,2}z_i))$, and flow rate from a compliant to non-compliant compartment is of the form $1 - 1/(1 + \exp(-a_{i,3} - a_{i,4}z_i))$. The parameter vector $a_i$ is assumed to be constant across the three levels of HbA1c levels in diagnosis group $i$. Rhee et al. (2005) show empirically that each effective interaction with a qualified care provider has an effect of decreasing the average HbA1c by 0.12% points. We assume that the same decrease is achievable for $i = 2, 3, 4$ with the first intervention over the base level.

Fitting of remaining parameters and transition rates. We make some additional assumptions about the other transition rates to simplify the estimation process. The progression rates for undiagnosed disease transitions ($f_{10,3}, f_{17,10}$) are fit by the least-squared parameter estimation process. Non-compliant compartments with the highest HbA1c levels are assumed to have the same disease progression rate as the undiagnosed cases ($f_{11,4} = f_{10,3}$ and $f_{18,11} = f_{17,10}$). We constrain the ratio of flow rates from high risk and low risk to IGT to be 4.1 so as to match the risk ratio from Mohan et al. (2008). For vertical flows within each of the three blocks (for each stage of disease) with six compartments each, we make assumptions about how the rates are linked. We assume that a given vertical flow in one block of six equals the flow rate of the analogous vertical flow in the other blocks of six. This transforms the fitting of 24 vertical flow parameters to the fitting of 8 vertical flow parameters. These assumptions together with relative risk ratios of disease progression summarized in Table 10 were used in fitting the other unknown flow rates.

Some caveats. The model uses point estimators and assumes deterministic flows, and thereby does not fully model parameter uncertainty and stochastic dynamics. The flows within a block of six compartments were set up to reproduce empirical HbA1c averages within a given disease state (IGT, early, late) as a function of intervention intensity and rather than representing the fraction of patients that comply or do not comply with best practice. Policies require knowledge of the full state of the system, including the fraction in each undiagnosed class, which is not typically available, and a full analysis of intervention portfolio
optimization with missing data would require further work. The results are based on a number of average phenomena that did not take advantage of cofactor data for the age, gender and other characteristics of individuals. The cost per intervention and their effects may depend on a number of factors not included in this paper, and numerical results demonstrate the approach but actual results may vary.