AUT Journal of Modeling and Simulation

AUT J. Model. Simul., 55(2) (2023) 215-226
DOI: 10.22060/miscj.2023.22294.5319

An Economic Prevention Plan for Alzheimer's Disease Based on Blood Biomarkers

Hanie Zand, Pooya Hoseinpour*

Department of Industrial Engineering & Management Systems, Amirkabir University of Technology (Tehran Polytechnic), Iran

ABSTRACT: This work presents a practical and cost-effective dynamic plan for preventing Alzheimer's disease. The plan involves periodic monitoring of an individual's blood biomarkers, personal characteristics, and budget constraints. The primary goal is to provide a feasible and realistic plan for each individual, with the highest likelihood of being followed. A Markov decision process model is proposed and solved using two algorithms: policy iteration and value iteration. In contrast to cerebrospinal fluid biomarkers, this plan relies on blood-based biomarkers, specifically Tau181 and APOE4, which are more cost-efficient and accessible for periodic testing. The interventions or actions within the model encompass choices between light or intense physical activity and adopting a less or more stringent diet. The decision model seeks to maximize the individual's quality of life while considering associated expenses. The proposed plan is tested on an modified dataset derived from clinical records, and it reveals insightful findings. Notably, our experimental study indicates that younger individuals at risk of the disease are more inclined to invest in preventive measures than those over 65. However, this trend does not apply to individuals lacking the APOE4 gene and those with higher tau181 concentration. The proposed plan can assist physicians in making appropriate recommendations.

Review History:

Received: Mar. 26, 2023
Revised: Oct. 18, 2023
Accepted: Nov. 05, 2023
Available Online: May, 30, 2024

Keywords:

Chronic Disease
Alzheimer's Prevention
Blood Biomarker
Quality of Life
Markov Decision Process

1- Introduction

Chronic diseases, which have long-lasting effects or treatments, are the leading causes of death and disability in many countries [1]. In 2015, 0.82% of people in the United Kingdom were diagnosed with dementia as a chronic disease, doubling over a decade. Chronic disease prevalence is expected to rise globally due to the aging population in the coming decades [2].

Alzheimer's disease is a chronic neurodegenerative condition and is the most common cause of dementia, accounting for up to 80% of all dementia cases and affecting up to 20% of individuals over the age of 80 [3]. While overall deaths from stroke and heart disease are decreasing in the United States, the proportion of deaths related to Alzheimer's disease is on the rise, reaching 89% in the past decade [4]. Alzheimer's disease is a progressive brain disorder that typically begins slowly and worsens over time. It is believed to initiate about twenty years before symptoms become visible [5]. Brain cells gradually deteriorate, leading to a continuous decline in memory and cognitive functions. In the early stages, individuals may experience difficulty with memory, but eventually, they may reach a point where they no longer recognize even the most significant people in their lives. Alzheimer's disease has recently garnered significant attention from various perspectives, including medicine, therapies, mortality outcomes, and economics.

Several factors contribute to the significance and increased risk associated with Alzheimer's disease. Firstly, it is an incurable disease that ultimately leads to death. Secondly, it represents a highly costly chronic disease. The substantial economic burden of Alzheimer's disease, particularly during the phases of treatment and progressive care, underscores the need for strategies that facilitate early detection and the slowing of disease progression [6].

For over 30 years, biomarkers have played a pivotal role in research and clinical practice related to neuronal degradation. Biomarkers serve as measurable indicators of a disease's biological or pathological status [7,8]. The two most accurate biomarkers for diagnosing Alzheimer's disease are beta-amyloid and tau proteins [9,10]. While these biomarkers in cerebrospinal fluid within the brain offer precision in Alzheimer's diagnosis, their high cost and limited availability hinder their use in diagnostic and screening procedures [11,12].

In recent years, researchers have identified similar biomarkers in blood that can aid in the early detection of Alzheimer's disease. The accessibility and cost-effectiveness of blood-based biomarkers make them appealing for clinical applications [11]. Among these, tau phosphorylated at threonine 181 (tau181) measured in blood plasma has emerged as a promising, scalable, and specific blood biomarker for Alzheimer's disease [13]. In addition to traditional

*Corresponding author's email: p.hoseinpour@aut.ac.ir

MRI scans, biomarkers play a crucial role in early disease diagnosis, enabling us to detect the disease even decades before the onset of symptoms. This early detection allows for the proposal of cost-effective and practical preventive interventions and actions.

This work implements a prevention plan based on periodic measurements of blood biomarkers, individual characteristics, conditions, and budget. The goal of this work is to offer a practical, attainable, and realistic prevention plan for patients, with a focus on enhancing the likelihood of adherence. In essence, we aim to address the question of how to provide Alzheimer's patients with a prevention plan that enables them to enjoy an improved quality of life while minimizing associated costs. We employ blood-based biomarkers instead of cerebrospinal fluid biomarkers, which are more readily available and cost-effective. Furthermore, our approach considers both the individual's quality of life and cost-related factors, accounting for disease prevention expenses and the positive physical effects that enhance quality of life. The proposed plan takes the form of an optimal policy within a Markov decision process model designed to delay disease progression. We evaluate this plan using a dataset that includes information from 1,091 Iranian individuals who were randomly selected. Of these individuals, 56% were women. The data was gathered from a specialized private center in this field and subsequently refined and modified by experts and specialists.

In the following, first, a review of prior works is presented in Section 2. In Section 3, the problem is stated and modeled. In Section 4, the numerical results of the constructed model are analyzed. Finally, Section 5 concludes the results and puts forward some directions for future research.

2- Related Works

Within the realm of chronic diseases, Alzheimer's has garnered significant attention from researchers due to its distinctive attributes. It follows a relentless progression, ultimately leading to mortality, and can only be postponed through continuous monitoring and long-term treatment. Regrettably, a considerable number of individuals are expected to contend with Alzheimer's disease in the future, as reported by [14], which, in turn, will have detrimental societal implications. Furthermore, the disease necessitates substantial costs for prevention and treatment, with expenses mounting as the disease advances in severity. While extensive research has been conducted on Alzheimer's disease, it has predominantly centered on disease detection [15]. In light of the escalating mortality rates and the exorbitant costs associated with the disease, the research focus is shifting toward the early prediction and prevention of the disease. Over the past few decades, there has been a substantial global effort directed at preventing Alzheimer's disease; see, e.g., [16] and the references therein.

[17] have shown that prevention is the only effective way to improve services and reduce the adverse effects of this disease, examining ineffective treatment methods and diagnostics. Given the importance of disease prevention, many works have offered solutions to prevent Alzheimer's disease. For example, [18] examined the effect of hormone replacement on the prevention of Alzheimer's. [19] presented a plan for early detection and prediction using deep learning tools. [20] proposed a three-year algorithm for prediction and early detection in the mild cognitive impairment phase. Besides MRI scans, which are traditionally done for early detection of the disease, biomarkers such as beta-amyloid and tau-protein play a crucial role in preventing disease, even decades before the onset of symptoms. For example, [21] developed a rapid and robust method for accurately quantifying structural changes in several areas of the brain by imaging and measuring biomarkers in the brain. [22] showed that accurate measurements of the biomarkers and comparing their concentrations with those of normal individuals are very effective in the early detection of the disease. [23] applied a neural network on biomarker data to predict Alzheimer's disease in the stage of mild cognitive impairment. In recent years, biomarkers have also shifted from biomarkers in the Cerebrospinal fluid to blood-based biomarkers. These biomarkers have been shown to be much more efficient. Moreover, tests such as MRI are less commonly used due to their high cost and lower availability. [11]stated that both Beta-amyloid and tau biomarkers accurately diagnose Alzheimer's disease pathology, which are also used in this study. In addition to the biomarkers, people's lifestyle is also essential in preventing the disease. For example, [24] studied the effects of a proper diet to prevent this disease. They found that diet is very effective in delaying and preventing Alzheimer's disease. [25] examined the effect of the Mediterranean diet and the use of vitamins such as vitamin D on the prevention of Alzheimer's disease. They found sufficient evidence to suggest this diet.

In recent years, the importance of Alzheimer's disease costs has been highlighted in various works. [26] examined the economic impact of Alzheimer's disease on Turkish society and concluded that the cost of Alzheimer's disease had become a significant issue in developed countries. [27] examined the costs of caring for Alzheimer's disease and the impact of its characteristics on those costs. [28] reviewed the direct and indirect costs of Alzheimer's disease. They found that different countries should strengthen their management, prevention, and treatment policies by examining disease characteristics and extensive research. [29] evaluated the social costs and resources used in Alzheimer's disease and the cognitive effects on cost.

Moreover, many studies on chronic diseases have employed Markov decision models. For instance, [30] utilized a Markov decision model to determine an optimal treatment policy for chronic ischemic heart disease. [31] offered a comprehensive review of cutting-edge models and methodologies applied in the context of chronic diseases. They also presented a tutorial on how to formulate and solve these critical issues, emphasizing specific challenges associated with chronic diseases like diabetes, heart disease, and cancer. They used Markov decision models to elucidate key considerations in model formulation. [1] conducted

a survey of the most commonly used methods, including Markov decision models, for healthcare decision-making in the realm of chronic diseases.

As mentioned, although extensive research has been done regarding the prevention of Alzheimer's disease, this disease still has many challenges at the expense of prevention and quality of life; specifically, no research has been done to address both yet, to the best of our knowledge. This work looks for an appropriate method to simultaneously address both aspects. The quality of life is ideal for everyone; however, the cost is an essential factor that can influence practical prevention actions followed by an individual.

3- The Proposed Plan

This section proposes a dynamic prevention plan in order to delay the onset or progression of Alzheimer's disease. As discussed, we recommend blood-based biomarkers testing which is more public and less expensive than Cerebrospinal fluid biomarkers. First, in Section 3-1, a discrete-time Markov decision process (MDP) is formulated, and then, in Section 3-2, policy iteration and value iteration algorithms are implemented to solve the model.

3- 1- Model Formulation

An MDP model is composed of several key components, including states, actions, transition probabilities, and a reward function. We will discuss each of these components in the following subsections.

3- 1- 1- States of the proposed MDP model

Our dataset comprises three key characteristics associated with 1,091 individuals under study:

- Age: includes two categories (age over 65 and age under 65; this age is critically advised by specialists in the field),
- APOE4 gene: includes two categories (having this gene and not having this gene),
- Tau181 concentration in blood: includes four categories (2-5), (5-18), (18-28), and (28-40).

APOE4 gene increases the risk of developing Alzheimer's disease [32] and blood Phosphorylated tau 181 is a recently-known biomarker (Karikari et al, 2020). All possible states, i.e., $S=\left(s_0,s_1,\ldots,s_{15}\right)$, can be summarized as in Table 1.

3- 1- 2- Actions of the proposed MDP model

In this study, we assess the influence of lifestyle choices on the prevention or delay of the onset and progression of Alzheimer's disease. Consequently, actions are determined

Table 1. States of the proposed MDP.

States	Age	gene APOE4	Tau181 concentration in blood
s_0	Under 65	✓	(2-5)
s_1	Under 65	✓	(5-18)
s_2	Under 65	✓	(18-28)
s_3	Under 65	✓	(28-40)
s_4	Under 65	×	(2-5)
s_5	Under 65	×	(5-18)
s_6	Under 65	×	(18-28)
s_7	Under 65	×	(28-40)
s_8	65 and over	✓	(2-5)
s_9	65 and over	✓	(5-18)
s_{10}	65 and over	✓	(18-28)
s_{11}	65 and over	✓	(28-40)
s_{12}	65 and over	×	(2-5)
s_{13}	65 and over	×	(5-18)
s_{14}	65 and over	×	(18-28)
s_{15}	65 and over	×	(28-40)

Table 2. Actions of MDP model.

Action	Exercise	Diet
a_0	Light	Poor
a_1	Light	Strong
a_2	Heavy	Poor
a_3	Heavy	Strong

based on the individual's lifestyle, with a particular focus on two key factors: exercise and diet. Research has shown that regular exercise and adhering to a Mediterranean diet can significantly reduce the progression of Alzheimer's disease [25].

Here, exercise is considered as either heavy or light, and diet is regarded as strong or poor. Heavy exercise refers to sports such as aerobics and vigorous bodybuilding exercises at least three times per week. A strong diet means using a Mediterranean diet in most daily meals. The actions, i.e., $A=(a_0,a_1,a_2,a_3)$, are determined and briefly presented in Table 2.

3- 1- 3- Transition probabilities of the proposed MDP model

The transition probability matrix represents the likelihood of transitioning from one state to another when a specific action is taken. In our case, there are 16 possible states for each individual, as outlined in Table 1, at each stage of the process. The values in the cells of the 16-by-16 matrix are calculated based on relative frequencies observed in the data. For example, to determine the transition probability from state one to state three under action four, we consider how many individuals are in state one and are taking action four, and then we calculate how many of them move to state three. The ratio of the number of individuals transitioning to state three to the total number in state one under action four represents the relative frequency and is assumed as the transition probability from state one to state three under action four. This process is repeated for all state-action-state combinations to populate the transition probability matrix.

Moreover, some transition probabilities are zero. This is because, for example, going from states that have the APOE4 gene to states that do not have this gene, and vice versa, is not possible. As a result, their probabilities are considered zero. The transition probabilities for going from state below 65 to above 65 are considered close to zero (given that among the people who refer with a very low probability, someone may be 64.5 years old to 65 years old who will go over 65 years old in the next round).

3- 1- 4- Reward function of the proposed MDP model

In this work, the reward function is considered to be an aggregated function of two terms, minimizing prevention cost and maximizing the quality of life. Indeed, the goal is to delay the onset or progression of Alzheimer's disease (i.e., to increase life quality) at a lower cost. The two terms are discussed in the following.

3-1-4-1 Action cost term

The actions in this study are combinations of exercise and diet, both incurring costs. Notably, the expenses for heavy and light exercise, as well as poor and strong diet programs, vary across countries and cities, leading to different outcomes. The primary objective is to propose a plan that factors in costs and life expectancy based on the specific conditions of each society. For this study, we have based the expenses on the costs of sports and diet programs in Miami, USA. Decisions are made every six months, with the approximate cost of light exercise being \$400 and heavy exercise being \$1300 for a six-month period. The cost for a weak diet is around \$200, while a strong diet costs approximately \$700 for the same period. We show action cost of action a_t by $c(a_t)$.

3-1-4-2 Quality of life reward term

To quantitatively calculate this reward term, an index called quality-adjusted life-years (QALY) has been used which is a common tool in health economic assessments [33]. This index shows how many years the patient will live according to her/his health status. The formula of this index is as follows:

$$QALY = years\ of\ delay \times health\ status$$

where The years of delay are calculated for each action taken, and the health status is represented by a number between 0 and 1. A higher value indicates an improved state of health and quality of life. As reported by [33], regular exercise every 6 months can potentially delay the progression of the disease by approximately 12 to 18 months. Therefore, in each decision period, the disease can be delayed by about 1 to 1.5 years through exercise. Additionally, it has been demonstrated that adhering to a proper Mediterranean diet (strong diet) for every 4.5 years can potentially reverse the disease by up to 7.5 years [35]. These values indicate that diet

Table 3. Maximum years of disease delay by exercise and diet in 6 months.

	Category	Years of delay in 6 months
Exercise	Light	0.95 year
	Heavy	1.5 year
Diet	Poor	0.52 year
	Strong	0.85 year

delays the disease 0.85 years every 6 months. The years of disease delay by exercise and diet in 6 months are reported in Table 3 (these values represent the maximum potential delay in disease progression achievable by taking each respective action)

Given that the health status varies across different patient states, with lower values indicating poorer health, these values are detailed in Table 4. Health status can be measured using standard questionnaires. In accordance with the methodology outlined by Prieto, L et al. (2013) the health status is assessed on a scale from 0 to 1; then have been validated by experts in the field.

Let define an indicator called Willingness to Pay (W2P) which shows how much each person is willing to pay to prevent Alzheimer's disease [34]. In our study, W2P is considered between 152$ and 158$ per month for Miami City. The willingness to pay varies depending on the patient's current state. In other words, the willingness to pay differs for each change in the patient's state. Therefore, the formula for obtaining the value of delaying onset or progression function of Alzheimer's disease (the quality-of-life cost term) can be calculated as W2P multiplied by QALY. We show W2P with β and QALY with q. Therefore, Reward function considering these two mentioned terms is as follows:

Table 4. Quality of life in each state.

States	Health status
s_0	0.9
s_1	0.7
s_2	0.4
s_3	0.1
s_4	0.95
s_5	0.9
s_6	0.6
s_7	0.3
s_8	0.8
s_9	0.5
s_{10}	0.2
s_{11}	0.05
s_{12}	0.9
s_{13}	0.7
s_{14}	0.4
s_{15}	0.1

$$r_t\left(s_t,a_t\right)=\beta\left(s_t\right)\times q\left(s_t,a_t\right)-c\left(a_t\right)$$

3- 1- 5- Optimality equations

Bellman optimality equations for the proposed MDP can be written as follows:

$$v_t\left(s_t\right)=\max_{a_t\in A\left(s_t\right)}\{r_t\left(s_t,a_t\right)+\gamma\sum_{s_{t+1}\in S}\Pr\left(s_{t+1}|s_t,a_t\right)v_{t+1}(s_{t+1})\}$$

$$v_T\left(s_T\right)=r_T\left(s_t\right),\ t\in T,s_t\in S,$$

where $v_t\left(s_t\right)$ is the expected reward value in stage $t\in T$ and $0<\gamma<1$ is the discount value. $r_t\left(s_t,a_t\right)$ is the reward of acting action a_t in state s_t defined in Section 3-1-4.

3- 2- Model Solving

The model we are considering in this paper is assumed to be unlimited (it means that the model runs until everybody passes away). This section provides the solution to the proposed Markov decision model using two algorithms: Policy Iteration and Value Iteration, which are detailed in the following Sections 4-1 and 4-2, respectively. It is worth noting that these algorithms are guaranteed to converge assuming $0<\gamma<1$.

3- 2- 1- Policy iteration

Let $\hat{\mu}_k$ denotes the selected policy in iteration k and $\hat{\mu}^*$ is the optimal policy. The main steps of the policy iteration algorithm are presented in Algorithm 1.

The equation that is solved in Step 2 is the bellman equation. In the policy iteration algorithm, first a desired policy is selected in the first iteration, and in the next step, that policy is evaluated by solving the Bellman equation and obtaining the value function vector (h^k). Then in the next step, using the value function vector obtained in the previous step, the policy is improved and a better policy is obtained. The resulting policy is then compared to the previous policy, if the output is the same, the algorithm is stopped and the resulting policy is the optimal policy; otherwise, it goes to the second step to repeat the algorithm.

3- 2- 2- Value iteration

The main steps of the value iteration algorithm are presented in Algorithm 2.

In the value iteration algorithm, first, an arbitrary value function vector is selected in the first iteration ($\vec{J}^1$), and in the next step, this vector is improved using based on the Bellman equation. Then examines whether the difference in amplitude of the obtained vector elements with the previous vector is less than a very small value and tends to zero. If this is the case, in the next step it obtains the optimal policy $d(i)$ for $i \in S$; otherwise, it goes to Step 2 to repeat the algorithm.

Both value iteration and policy iteration algorithms are

Algorithm 1: Policy Iteration

1. Set $k = 1$ and select an initial policy of $\hat{\mu}_k$.
2. Solve the following set of equations for $= 1, 2, \dots, |S|$.

$$h_i^k = \bar{r}\big(i, \mu_k(i)\big) + \gamma \sum_{j=1}^{S} \Pr(i, \mu_k(i), j) h_j^k$$

3. Select the new policy $\hat{\mu}_{k+1}$ by:

$$\hat{\mu}_{k+1}(i) = \underset{a \in A(i)}{\operatorname{argmax}} \left\{ \bar{r}(i,a) + \gamma \sum_{j=1}^{S} \Pr(i,a,j) h_j^k \right\}$$

4. If the new policy is the same as the previous policy, (if, $\hat{\mu}_K(i) = \hat{\mu}_{K+1}(i)$, for each $i \in S$, then stop and set $\hat{\mu}^*(i) = \hat{\mu}_K(i)$. Otherwise, set $k \leftarrow k + 1$ and go to Step 2.

Algorithm 2: Value Iteration

1. Set $k = 1$. Then set arbitrary values for $\vec{J}^k$, a vector of size $|S|$. Put $\varepsilon > 0$.
2. Calculate the value of the following equation for each $i \in S$:

$$\vec{J}^{k+1} \leftarrow \max_{a \in A(i)} \left\{ \bar{r}(i,a) + \gamma \sum_{j=1}^{|S|} \Pr(i,a,j) J_j^k \right\}$$

3. If $\left\| \vec{J}^{k+1} - \vec{J}^k \right\| < \varepsilon(1-\gamma)/2\gamma$ go to step 4; otherwise set $k \leftarrow k + 1$ and go to Step 2.
4. For each $i \in S$ choose

$$d(i) = \underset{a \in A(i)}{\operatorname{argmax}} \left\{ \bar{r}(i,a) + \gamma \sum_{j=1}^{|S|} P(i,\ a, j) J_{(j)}^k \right\}$$

and stop the algorithm.

Table 5. Numerical experiment result.

State	Selected action for each state in optimal policy	Expected of immediate reward for each state in optimal policy	ICER
s_0	a_0	356.35	1154
s_1	a_3	1190.71	1163
s_2	a_3	1561.86	1047
s_3	a_1	2248.59	611
s_4	a_3	1210.75	1156
s_5	a_3	1573.03	1042
s_6	a_3	3850.47	637
s_7	a_3	2343.79	858
s_8	a_0	499.3	1000
s_9	a_0	861.07	759
s_{10}	a_1	1680.75	733
s_{11}	a_3	2353.45	855
s_{12}	a_0	659.94	882
s_{13}	a_3	1405.98	1093
s_{14}	a_3	1815.3	976
s_{15}	a_3	2347.82	855

guaranteed to converge to the optimal policy, so it is expected that we get similar policies from both algorithms; however, considering the higher speed of the policy iteration algorithm, it might be better to use this algorithm.

4- Results

The dataset under study comprises information from 1,091 individuals, including features like genes, age, and biomarker concentrations both at present and six months later. Key individual characteristics, including the presence of the APOE4 gene and biomarker concentration ranges, were sourced from [11] and [8]. Additional information, such as changes in blood biomarker concentrations and the potential for reducing these concentrations, was gathered through interviews with experts in the field. Both proposed algorithms, i.e., policy iteration and value iteration, are implemented in a Python environment running on a dual-core PC with a 2.20GHz processor, and 16GB RAM running on a 64-bit Window 10. Each one of the algorithms can be used to solve the model; however, the policy iteration algorithm is much more efficient and preferable. The results of our numerical results and sensitivity analyses are reported in the following subsections.

4- 1- Numerical Results

The proposed algorithms in Section 4 have been implemented with a discount rate of $\gamma = 0.5$. The optimal policy has been obtained and reported in Table 5. The Table reports the amount of expected immediate reward for each pair of states and action in optimal policy. It is important to note that the obtained optimal policy is based on the specific conditions and costs associated with the actions. These costs, which include the expenses related to exercise and diet programs, can vary significantly from one city to another. As previously mentioned, the costs presented in this study are based on the rates in Miami, United States. The last column of the table reports the Incremental Cost-Effectiveness Ratio (ICER) which shows the cost value per unit of QALY.

Table 5 reveals several interesting insights. It suggests that individuals under the age of 65 typically prefer more expensive preventive actions compared to those over 65. However, this trend does not hold for individuals without the APOE4 gene and with higher tau181 concentration, as they tend to choose more costly actions. These variations may be linked to differences in life expectancy between these groups. In terms of ICER, it is generally lower for older individuals than those under 65, indicating that older individuals benefit from more cost-effective preventive actions, despite the higher expense. Regarding biomarker concentration, the typical expectation is that individuals with higher tau181 concentration would be more willing to invest in costly actions. However, this pattern does not always hold, possibly due to the complex interplay between the APOE4 gene and biomarker levels. In summary, the choice of preventive actions is influenced by age, genetic factors (APOE4 gene), and biomarker concentration, resulting in variations in the cost-effectiveness of different strategies.

4- 2- Sensitivity Analyses

4- 2- 1- Sensitivity analysis on weight of cost term

In this section, the weight of cost in the objective function is increased from 5% to 50%, and the results are reported in

Table 6. Results related to the effect of cost weight changes

Percentage of increase in cost weight	Results (optimal policy)	Average of action number of policies	Action Index
0%	(0, 3, 3, 1, 3, 3, 3, 3, 0, 0, 1, 3, 0, 3, 3, 3)	2.00	0.67
5%	(0, 3, 1, 1, 3, 3, 0, 2, 0, 0, 1, 3, 0, 1, 0, 3)	1.44	0.48
10%	(0, 3, 0, 1, 3, 3, 0, 1, 0, 0, 0, 1, 0, 0, 0, 1)	0.81	0.27
15%	(0, 3, 0, 0, 3, 3, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)	0.56	0.19
20%	(0, 0, 0, 0, 3, 3, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)	0.37	0.12
25%	(0, 0, 0, 0, 3, 3, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)	0.19	0.06
30%	(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)	0	0
35%	(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)	0	0
40%	(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)	0	0
45%	(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)	0	0
50%	(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)	0	0

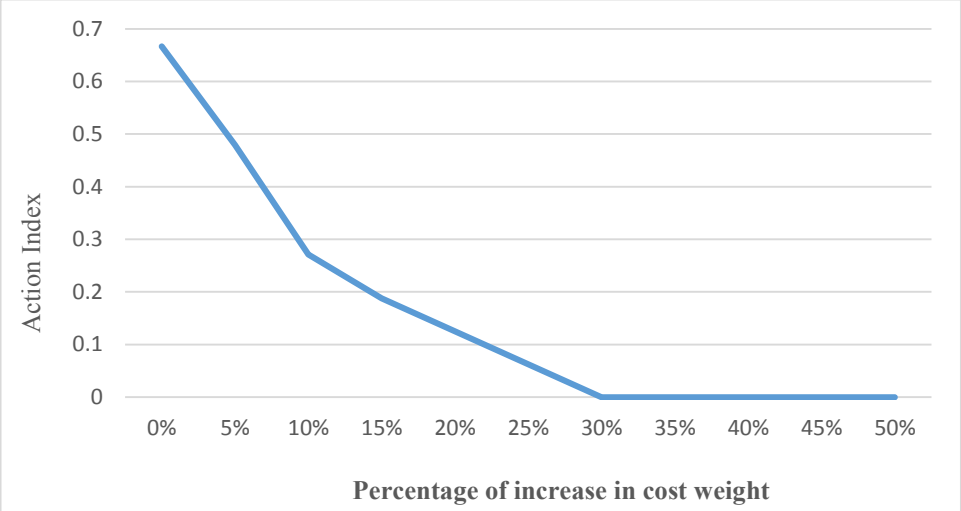

Fig. 1. Relationship between action index and percentage of cost weight.

Table 6.

The zero percent in Table 6 is the same as the result of the numerical experiment reported in Table 5. For each percentage value, we obtain the optimal policy and calculate the average number of actions for each policy. Finally, we normalize this average by dividing it by 3, which represents the range of action numbers, and convert it to values within the range of 0 to 1. These values are used as an action index and are reported in the last column of the table. The closer this index is to zero, the closer the average number of actions in a policy is to 0. Conversely, an action index of 1 means that all the actions in a policy are set to 3 (indicating that action a_3 is selected in every state). Furthermore, an action index of 0 implies that all the actions in a policy are set to 0 (indicating that action a_0 is selected in every state). Figure 1 illustrates the relationship between the percentage increase in cost weight and the aforementioned action index.

As the percentage of cost weight increases, while the lifetime weight remains fixed, the action index tends to zero. This indicates that the optimal policy tends to select actions with fewer numbers and lower costs. In other words, when the

Table 7. Results related to the effect of lifetime weight changes

Percentage of increase in lifetime weight	Results (optimal policy)	Average of action number of policies	Action Index
0%	(0, 3, 3, 1, 3, 3, 3, 3, 0, 0, 1, 3, 0, 3, 3, 3)	2	0.67
5%	(0, 3, 3, 2, 3, 3, 2, 3, 0, 0, 1, 3, 0, 3, 3, 3)	2	0.67
10%	(3, 3, 3, 3, 3, 3, 3, 3, 0, 0, 3, 3, 0, 3, 3, 3)	2.44	0.81
15%	(3, 3, 3, 3, 3, 3, 3, 3, 0, 0, 3, 3, 0, 3, 3, 3)	2.44	0.81
20%	(3, 3, 3, 3, 3, 3, 3, 3, 0, 3, 3, 3, 0, 3, 3, 3)	2.62	0.87
25%	(3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 0, 3, 3, 3)	2.81	0.94
30%	(3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3)	3	1
35%	(3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3)	3	1
40%	(3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3)	3	1
45%	(3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3)	3	1
50%	(3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3)	3	1

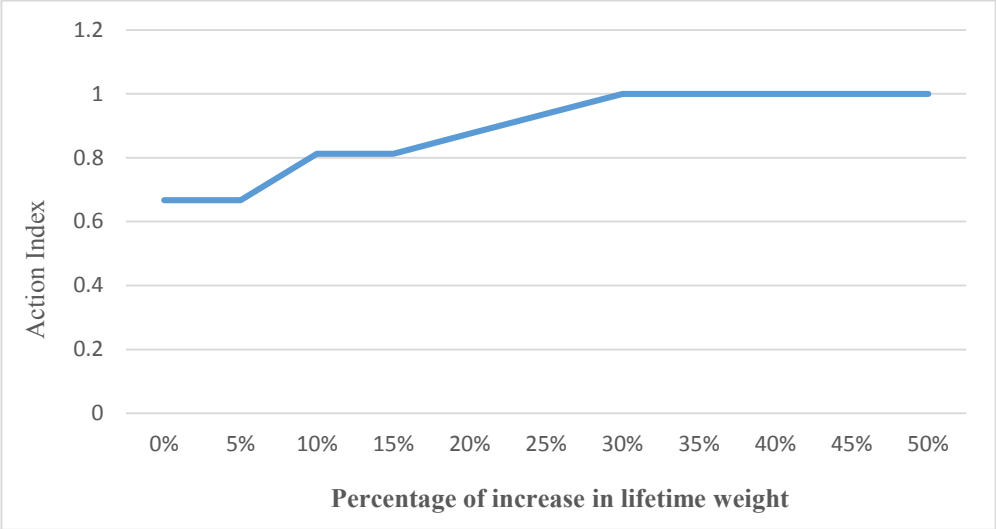

Fig. 2. Relationship between action index and higher percentage of lifetime weight

cost function is given more weight, it becomes more crucial to the individual, and it may be economically challenging or even impossible to afford costly actions. Consequently, the optimal policy suggests actions that are more aligned with the individual's financial situation, prioritizing lower-cost options.

4- 2- 2- Sensitivity analysis on weight of lifetime reward term

In this section, the weight of lifetime in the objective function is increased from 5% to 50%, and the results are reported in Table 7.

As in the previous section, the action index for longevity was obtained and the results can be seen in Table 8. Figure 2 shows the relationship between the percentage of lifetime weight and the action index.

As depicted in Figure 2, when the percentage of the lifetime weight increases (while the cost weight remains fixed), the action index tends to 1. This indicates that the optimal policy leans toward selecting actions with more options and higher costs. The rationale behind this shift may be that a higher weight on lifetime values longevity as more critical to the individual than cost. In such cases, the person is

Table 8. Results of discount rate change

Discount rate	Results (optimal policy)	Average of action number of policies	Action Index
0.05	(3, 3, 3, 3, 3, 3, 3, 3, 0, 0, 3, 3, 0, 3, 3, 3)	2.44	0.81
0.15	(3, 3, 3, 3, 3, 3, 3, 3, 0, 0, 3, 3, 0, 3, 3, 3)	2.44	0.81
0.25	(0, 3, 3, 3, 3, 3, 3, 3, 0, 0, 1, 3, 0, 3, 3, 3)	2,12	0.71
0.35	(0, 3, 3, 3, 3, 3, 3, 3, 0, 0, 1, 3, 0, 3, 3, 3)	2,12	0.71
0.45	(0, 3, 3, 3, 3, 3, 3, 3, 0, 0, 1, 3, 0, 3, 3, 3)	2,12	0.71
0.55	(0, 3, 0, 1, 3, 3, 3, 1, 0, 0, 1, 3, 0, 3, 3, 3)	1.69	0.56
0.65	(0, 3, 0, 1, 3, 3, 3, 1, 0, 0, 1, 3, 0, 3, 3, 3)	1.69	0.56
0.75	(0, 3, 0, 1, 3, 3, 1, 1, 0, 0, 1, 3, 0, 3, 0, 3)	1.37	0.46
0.85	(0, 3, 0, 1, 3, 3, 0, 1, 0, 0, 0, 1, 0, 3, 0, 1)	1	0.33
0.95	(0,0, 0, 1, 3, 3, 0, 1, 0, 0, 0, 1, 0, 0, 0, 1)	0.62	0.27

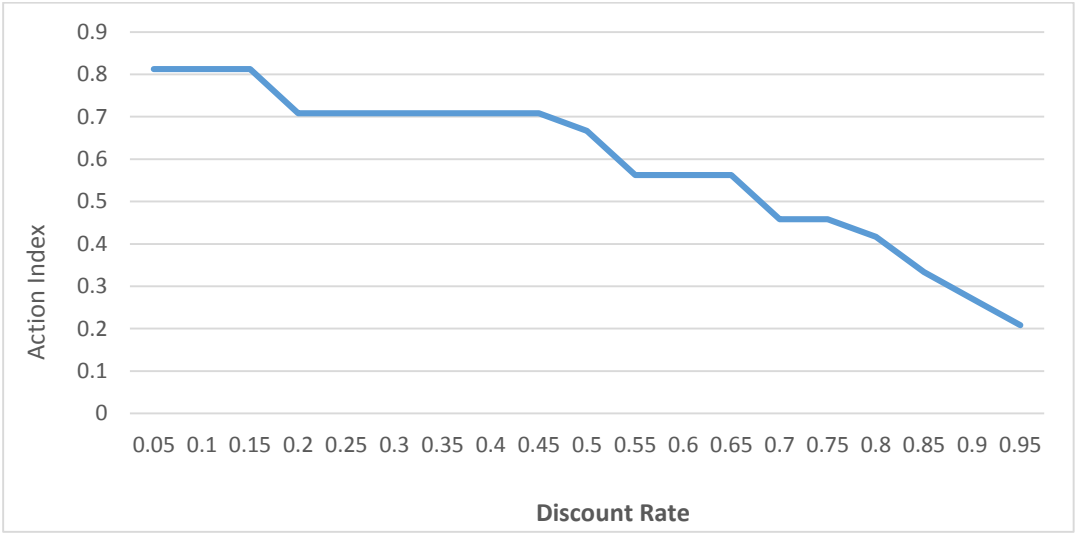

Fig. 3. Relationship between the discount rate and the action index.

willing to pay more without financial constraints and prefers actions that maximize their lifetime. Therefore, the optimal policy prioritizes higher-cost actions in this scenario.

4- 2- 3- Sensitivity analysis on the discount rate

The discount rate essentially determines the importance an individual assigns to future rewards compared to immediate rewards. A discount rate of zero indicates that the individual is myopic and only values immediate rewards, while a rate of one signifies that the individual evaluates their actions based on the cumulative future rewards [22]. In this section, we discuss the results related to different discount rates. By modifying the discount rate in the algorithms used to solve the primary model, we obtain results and optimal policies. Subsequently, by analyzing the number of optimal policies, we calculate the action index. Finally, we examine the relationship between the discount rate and the action index. Refer to the results in Table 8. The relationship between the discount rate and action index has been visualized in Figure 3.

As shown in Figure 3, the higher the discount rate, the lower the action index. This implies that the optimal policy favors actions with a higher number. Essentially, the discount rate reflects the individual's preference for receiving rewards in the near future compared to the distant future. A higher

discount rate suggests that immediate rewards are more important, leading individuals to choose actions with a higher number and greater cost. In other words, when time is a crucial factor, individuals are more willing to pay more for quicker results. In summary, this analysis underscores the significance of cost in medical decision-making. It demonstrates that cost is a critical factor that influences the choices individuals make when considering preventive actions and their timing.

5- Conclusion

In this study, we have proposed an optimal prevention plan for Alzheimer's disease that addresses the dual concerns of enhancing quality of life and minimizing associated costs. Our approach involves a Markov decision process model, personalized for each patient, with a focus on blood-based biomarkers, including Tau181, APOE4 status, and age. The interventions or actions recommended encompass light or strong physical activity and poor or strong dietary changes. The model incorporates adherence by considering the financial costs incurred as part of the decision-making process. One noteworthy aspect of our model is the utilization of blood biomarkers instead of the more expensive and less accessible Cerebrospinal fluid biomarkers. Blood biomarkers can be tested periodically, offering a more practical approach compared to MRI and PET scans. Furthermore, the model takes into account both quality of life and cost considerations within the objective function and seeks to strike a balance between these factors. To solve the model, we have employed two algorithms, policy iteration, and value iteration. Our experimental study reveals that people are more interested in investing in preventive plans during the pre-disease or early stages of Alzheimer's, but their motivation decreases as the disease progresses to more advanced stages. We have demonstrated that by considering the cost factor and the positive physical effects of preventive measures, the proposed plan becomes more realistic and pragmatic. Furthermore, we have conducted various sensitivity analyses to explore the impact of the objective function's components, including quality of life and costs, as well as the discount rate on the optimal policy.

For future research, it would be interesting to delve into multi-objective planning and introduce uncertainty modeling in the reward function. Additionally, extending the model to include a broader range of states and preventive actions, such as social activation, cognitive training, and the management of treatable clinical risk factors, could provide valuable insights into comprehensive strategies for addressing Alzheimer's disease.

References

[1] Ahlskog, J. E., Geda, Y. E., Graff-Radford, N. R., & Petersen, R. C. (2011). Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. In Mayo clinic proceedings, 86(9), 876-884.

[2] Alzheimer's Association. (2017). Alzheimer's disease facts and figures. Alzheimer's & Dementia, 13(4), 325-373.

[3] Bartochowski, Z., Conway, J., Wallach, Y., Chakkamparambil, B., Alakkassery, S., & Grossberg, G. T. (2020). Dietary interventions to prevent or delay alzheimer's disease: what the evidence shows. Current Nutrition Reports, 1-16.

[4] Basu, R. (2013). Willingness-to-pay to prevent Alzheimer's disease: a contingent valuation approach. International journal of health care finance and economics, 13(3-4), 233-245.

[5] Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. Alzheimer's & dementia, 3(3), 186-191.

[6] Canter, R. G., Penney, J., & Tsai, L. H. (2016). The road to restoring neural circuits for the treatment of Alzheimer's disease. Nature, 539(7628), 187-196.

[7] Castro, D. M., Dillon, C., Machnicki, G., & Allegri, R. F. (2010). The economic cost of Alzheimer's disease: Family or public-health burden? Dementia & Neuropsychologia, 4(4), 262-267.

[8] Crous-Bou, M., Minguillón, C., Gramunt, N., & Molinuevo, J. L. (2017). Alzheimer's disease prevention: from risk factors to early intervention. Alzheimer's research & therapy, 9(1), 1-9.

[9] Denton, B. T. (2018). Optimization of sequential decision making for chronic diseases: From data to decisions. In Recent Advances in Optimization and Modeling of Contemporary Problems (pp. 316-348). INFORMS.

[10] Donegan, K., Fox, N., Black, N., Livingston, G., Banerjee, S., & Burns, A. (2017). Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. The Lancet Public Health, 2(3), e149-e156.

[11] Fan, L., Mao, C., Hu, X., Zhang, S., Yang, Z., Hu, Z., ... & Xu, Y. (2020). New insights into the pathogenesis of Alzheimer's disease. Frontiers in neurology, 10, 1312.

[12] Fillit, H. M. (2002). The role of hormone replacement therapy in the prevention of Alzheimer disease. Archives of Internal Medicine, 162(17), 1934-1942.

[13] Grassi, M., Perna, G., Caldirola, D., Schruers, K., Duara, R., & Loewenstein, D. A. (2018). A clinically-translatable machine learning algorithm for the prediction of Alzheimer's disease conversion in individuals with mild and premild cognitive impairment. Journal of Alzheimer's Disease, 61(4), 1555-1573.

[14] Holland, D., Brewer, J. B., Hagler, D. J., Fennema-Notestine, C., Dale, A. M., & Alzheimer's Disease Neuroimaging Initiative. (2009). Subregional neuroanatomical change as a biomarker for Alzheimer's disease. Proceedings of the National Academy of Sciences, 106(49), 20954-20959.

[15] Karikari, T. K., Pascoal, T. A., Ashton, N. J., Janelidze, S., Benedet, A. L., Rodriguez, J. L., ... & Blennow, K. (2020). Blood phosphorylated tau 181 as a biomarker

for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. The Lancet Neurology, 19(5), 422-433.

[16] Kepka, A., Ochocinska, A., Borzym-Kluczyk, M., Skorupa, E., Stasiewicz-Jarocka, B., Chojnowska, S., & Waszkiewicz, N. (2020). Preventive role of L-Carnitine and balanced diet in Alzheimer's disease. Nutrients, 12(7), 1987.

[17] J. Viña, J. Sanz-Ros, Alzheimer's disease: only prevention makes sense. European journal of clinical investigation, 48(10) (2018), e13005.

[18] Liu, S., Liu, S., Cai, W., Pujol, S., Kikinis, R., & Feng, D. (2014). Early diagnosis of Alzheimer's disease with deep learning. In 2014 IEEE 11th international symposium on biomedical imaging (ISBI), 1015-1018. IEEE.

[19] Moscoso, A., Grothe, M. J., Ashton, N. J., Karikari, T. K., Rodriguez, J. L., Snellman, A., ... & Alzheimer's Disease Neuroimaging Initiative. (2021). Time course of phosphorylated-tau181 in blood across the Alzheimer's disease spectrum. Brain, 144(1), 325-339.

[20] Murad, A. L. (2019). 15 simple diet tweaks that could cut your Alzheimer's risk. https://www.mayoclinic.org/.

[21] Prieto, L., & Sacristán, J. A. (2003). Problems and solutions in calculating quality-adjusted life years (QALYs). Health and quality of life outcomes, 1, 1-8.

[22] Nakamura, A. (2018). plasma biomarker for Alzheimer's disease: are we ready now for clinical practice and drug trials? The Journal of Prevention of Alzheimer's Disease, 5, 158-159.

[23] Ning, K., Chen, B., Sun, F., Hobel, Z., Zhao, L., Matloff, W., ... & Alzheimer's Disease Neuroimaging Initiative. (2018). Classifying Alzheimer's disease with brain imaging and genetic data using a neural network framework. Neurobiology of aging, 68, 151-158.

[24] Rapp, T., Andrieu, S., Chartier, F., Deberdt, W., Reed, C., Belger, M., & Vellas, B. (2018). Resource use and cost of alzheimer's disease in France: 18-month results from the GERAS observational study. Value in Health, 21(3), 295-303.

[25] Rive, B., Grishchenko, M., Guilhaume–Goulant, C., Katona, C., Livingston, G., Lamure, M.,... & Francois, C. (2010). Cost effectiveness of memantine in Alzheimer's disease in the UK. Journal of medical economics, 13(2), 371-380.

[26] Safieh, M., Korczyn, A. D., & Michaelson, D. M. (2019). ApoE4: an emerging therapeutic target for Alzheimer's disease. BMC medicine, 17(1), 1-17.

[27] Shen, X. N., Li, J. Q., Wang, H. F., Li, H. Q., Huang, Y. Y., Yang, Y. X., ... & Alzheimer's Disease Neuroimaging Initiative. (2020). Plasma amyloid, tau, and neurodegeneration biomarker profiles predict Alzheimer's disease pathology and clinical progression in older adults without dementia. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 12(1), e12104.

[28] Stone, R. I. (2001). Alzheimer's disease and related dementias: important policy issues. Aging & mental health, 5(1), 146-148.

[29] Toledo, J. B., Zetterberg, H., Van Harten, A. C., Glodzik, L., Martinez-Lage, P., Bocchio-Chiavetto, L., ... & Trojanowski, J. Q. (2015). Alzheimer's disease cerebrospinal fluid biomarker in cognitively normal subjects. Brain, 138(9), 2701-2715.

[30] Toombs, J., & Zetterberg, H. (2020). In the blood: Biomarkers for amyloid pathology and neurodegeneration in Alzheimer's disease. Brain Communications, 2(1), fcaa054.

[31] L.N. Steimle, B.T. Denton, Markov decision processes for screening and treatment of chronic diseases. Markov Decision Processes in Practice, (2017) 189-222.

[32] Udeh-Momoh, C., Zheng, B., Sandebring-Matton, A., Novak, G., Kivipelto, M., Jönsson, L., & Middleton, L. (2022). Blood Derived Amyloid Biomarkers for Alzheimer's Disease Prevention. The Journal of Prevention of Alzheimer's Disease, 9(1), 12-21.

[33] Vozikis, A., Goulionis, J. E., & Benos, V. K. (2012). The partially observable Markov decision processes in healthcare: an application to patients with ischemic heart disease (IHD). Operational Research, 12, 3-14.

[34] Yu, J. T., Xu, W., Tan, C. C., Andrieu, S., Suckling, J., Evangelou, E., ... & Vellas, B. (2020). Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. Journal of Neurology, Neurosurgery & Psychiatry, 91(11), 1201-1209.

[35] Zencir, M., Kuzu, N., Beşer, N. G., Ergin, A., Çatak, B., & Şahiner, T. (2005). Cost of Alzheimer's disease in a developing country setting. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences, 20(7), 616-622.

[36] Zhu, C. W., Scarmeas, N., Torgan, R., Albert, M., Brandt, J., Blacker, D., ... & Stern, Y. (2006). Clinical characteristics and longitudinal changes of informal cost of Alzheimer's disease in the community. Journal of the American Geriatrics Society, 54(10), 1596-1602.

HOW TO CITE THIS ARTICLE

H. Zand, P. Hoseinpour, An Economic Prevention Plan for Alzheimer's Disease Based on Blood Biomarkers, AUT J. Model. Simul., 55(2) (2023) 215-226.

DOI: 10.22060/miscj.2023.22294.5319