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published in

Demografie, Review for Population Research [translation of journal of Czech Statistical Office]
2021

DOI (link to publisher)

[10.54694/DEM.0287](https://doi.org/10.54694/DEM.0287)

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Broulíková, H. M., Kučera, M., & Arltová, M. (2021). THE TIMELY DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE: MICROSIMULATING COST-EFFECTIVENESS IN THE CZECH REPUBLIC. *Demografie, Review for Population Research [translation of journal of Czech Statistical Office]*, 63(4), 216-225. <https://doi.org/10.54694/DEM.0287>

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THE TIMELY DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE: MICROSIMULATING COST-EFFECTIVENESS IN THE CZECH REPUBLIC

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Abstract

Using a microsimulation model, this study evaluates the cost-effectiveness of a hypothetical policy that would increase diagnosis and treatment availability for people at an early stage of Alzheimer's disease in the Czech Republic. If widely available, timely diagnosis and treatment would represent a dominant strategy bringing net benefit of EUR 13,751 per lifetime of each person living with this disease.

Keywords: Alzheimer's disease, cost-effectiveness, timely diagnosis, Czech Republic, dementia

<https://doi.org/10.54694/dem.0287>

Demografie, 2021, 63 (4): 216–225

INTRODUCTION

The Czech population has been significantly ageing. According to the Czech Statistical Office, 26% of the population in the Czech Republic in 2019 was over the age of 60 (CZSO, 2020). This number increased by 9% since 1980 and it is expected to grow over time and reaching 37% by 2050 (UN, 2018). One of the difficulties closely associated with ageing is the decline in cognitive functions (Murman, 2015), which could lead to dementia, a syndrome defined by progressive impairments to memory, thinking, and behaviour that affect people's ability to look after

themselves (WHO, 2020). Alzheimer's disease (AD) is the most common cause of dementia, accounting for about 60% of all cases (WHO, 2020). Owing to the increasing prevalence of dementia and the associated emotional and economic burden it causes, the World Health Organization (WHO) has recognised dementia as a public health priority (World Health Organization, 2012).

According to Mátl *et al.* (2016), the number of people living with dementia in the Czech Republic reached 156,000 in 2015. This figure is in line with the upper limit of an estimate published by the Institute

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for Health Metrics and Evaluation (2019), which reported that there were 135,738 cases in 2015 with a corresponding 95% confidence interval (CI), of 118,821 – 154,936, 139,042 cases in 2016 (CI 121,407 – 159,145), and 142,442 cases in 2017 (CI 124,351 – 163,151). The prevalence of dementia has been estimated to reach 250,000 by 2050 (Holmerová – Hort *et al.*, 2017).

The last two decades witnessed a sharp drop in the share of people living with undiagnosed dementia. According to Waldemar *et al.* (2007), the rate of diagnosis in 2004 was only 9%. Mátl *et al.* (2016) report that 6% of people living with dementia received inpatient and 24% outpatient care in 2015. Most recently, the official health statistics derived from the national health-care register revealed that there were 102,000 people living with dementia in 2017, suggesting that up to 72% of people living with dementia receive a diagnosis (World Health Organization, 2019, Ministry of Health of the Czech Republic 2021). Although these figures suggest that there has recently been a dramatic decrease in the treatment gap – from 91% in 2004 to 28% in 2017 – part of the drop has likely been brought about by an improvement in the availability of reliable data on the number of treated cases.

Nevertheless, the diagnosis gap has two dimensions: one is *whether* a person has received a diagnosis and the other is the *timing* of the diagnosis. In contrast to the improvements in obtaining a diagnosis, late diagnosis remains a major problem in the country. According to a case study, 56% of people admitted to hospital with dementia had received no diagnosis or treatment prior to being hospitalised for this reason. At the same time, 50% of these hospitalised patients had already progressed to a moderate and 42% to a severe stage of dementia (Lužný *et al.*, 2014). The late diagnosis hypothesis is further documented by the short survival of people with dementia: 44% die within one year, and only 16% live longer than five years from the dementia diagnosis (Broulíková *et al.*, 2020). The unavailability of timely diagnosis and post-diagnostic support is recognised in the recently adopted National Action Plan for Alzheimer's Disease and Related Illnesses (Ministry of Health of the Czech Republic, 2021), the first strategic objective of which focuses on remedying this situation.

Dementia is associated with substantial health and social care costs. Care for Alzheimer's and related forms of dementia was estimated to cost USD 818 billion worldwide in 2016 (Prince *et al.*, 2015) and 44.7 billion Czech Koruna (USD 2 billion) in the Czech Republic in 2015 (Mátl *et al.*, 2016). The high costs associated with the disease are mainly driven by informal caregiving and social care (Winblad *et al.* 2016), but people with dementia also face costly adverse health events leading to high hospitalisation rates (Bernardes *et al.*, 2018). Modelling studies suggest that the timely treatment of Alzheimer's disease could increase patients' utility while decreasing their lifetime costs. Weimer and Sager (2009) estimated that timely detection and treatment in the United States resulted in net social benefits of USD 94,000 and governmental fiscal savings of USD 15,000 per patient's lifetime (Weimer – Sager, 2009). For the United Kingdom, Getsios *et al.* (2012) suggest more modest but still substantial societal savings of GBP 5,700 (USD 8,400) and a decrease in medical costs of GBP 2,100 (USD 3,100). In the Czech Republic, a study focusing on the effect of timely diagnosis on lifetime costs estimated that the savings from timely diagnosis could amount as much as EUR 26,000, depending on the person's age at the disease's onset and the person's cognitive score at the time of diagnosis (Broulíková *et al.*, 2018).

The present microsimulation study builds on the previous model by Broulíková *et al.* (2018) and provides comprehensive insight into the cost-effectiveness of the timely diagnosis and treatment of AD in the Czech Republic. Unlike the previous study, we derive the demographic composition of the Czech population living with AD from the national health-care registers. This step provides valuable information about the demographics of people living with AD in the country, and, importantly, allows us to appropriately address heterogeneity of the population as well as the uncertainty of the results. Moreover, to evaluate cost-effectiveness, we study both the effects of the timely diagnosis on costs and the quality of life of people living with AD.

DATA AND METHODS

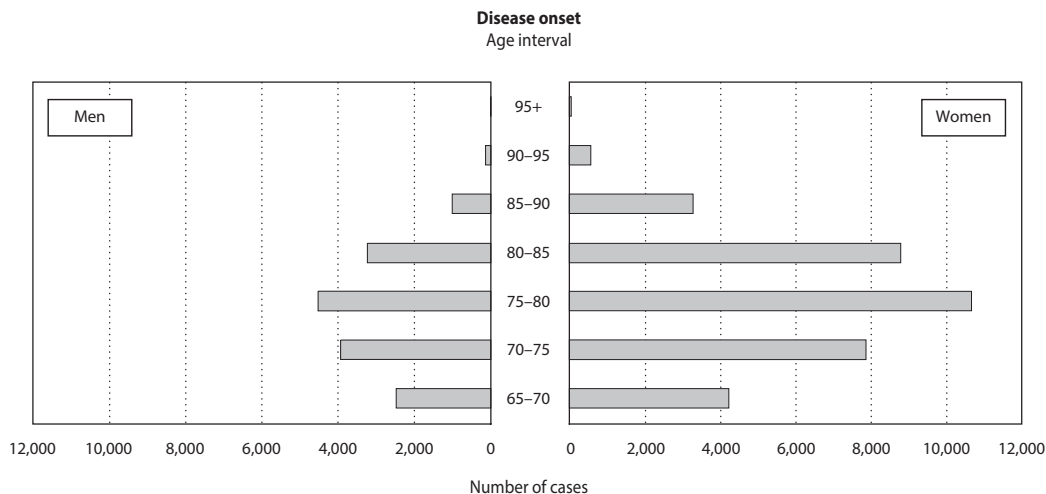
People living with AD in the Czech Republic

Our study modelled a heterogeneous cohort of 100,000 people with incident AD. Given that no official data

stratified by age and gender on the incidence of AD in the Czech Republic have been published, we derived this information by combining data from the national health-care register with estimates of the time between onset of the disease and diagnosis in the country. First, all patients with an AD diagnosis

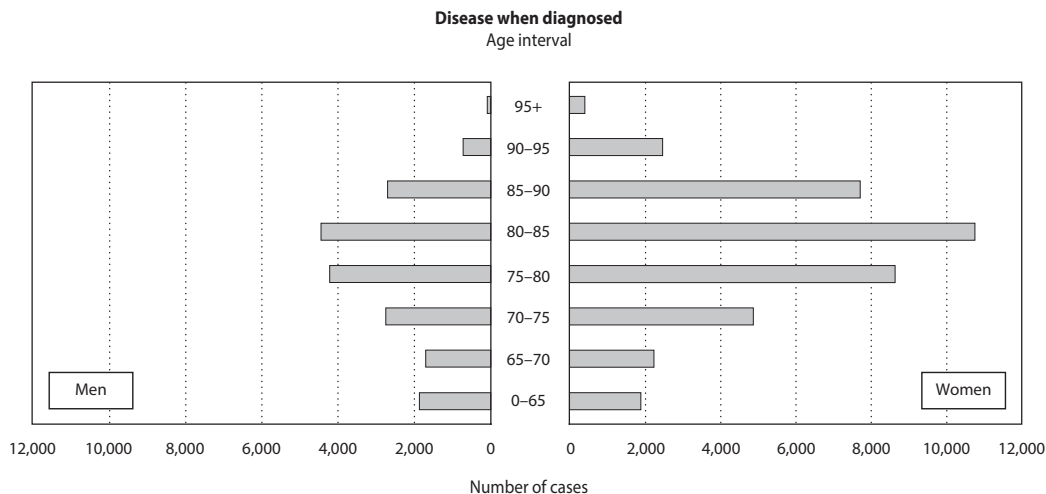
that was made between 1994 and 2014 were filtered from the National Register of Hospitalised Patients maintained by the Institute of Health Information and Statistics. The data source and filtering strategy are described in detail elsewhere (Brouliková *et al.*, 2020). Second, to account for the discrepancy between

Figure 1a Age and gender structure of patients with Alzheimer’s disease at the disease onset



Source of data: Nationwide Register of Hospitalized Patients, author’s calculation.

Figure 1b Age and gender structure of patients with Alzheimer’s disease when diagnosed



Source of data: Nationwide Register of Hospitalized Patients, author’s calculation.

the time of the disease's onset and its official diagnosis, we simulated the mean time of untreated patients' cognitive decline from point of the disease's onset to moderate cognitive deficit and shifted the age of the identified these people accordingly, i.e. by 3.8 years. The moment of the disease's onset is conceptualised as a drop of the Mini mental examination score (Folstein *et al.*, 1975) to 28 points (Getsios *et al.*, 2012), and we assume that in the Czech Republic a diagnosis is made when the score drops to 15 points, which is the middle of the moderate disease phase. Third, to retain only the ages typical for AD's manifestation, we excluded 6,715 patients under the age of 65 at the approximate time of the disease's onset.

Figures 1a and 1b present the age and gender structure of patients with Alzheimer's disease at the moment of the disease's onset and at the time of diagnosis (i.e. when first recorded in the register). There were 57,559 (68% women) people living with AD identified in the register. The mean and median age was 78.5 and 80 years, respectively. After the adjustment for the delay in diagnosis and after removing those under the age of 65 years at the disease's onset, the number of people included decreased to 50,844 (70% women). The mean and median age decreased to 76.8 and 77 years, respectively. Out of this population, we sampled 100,000 people to receive a cohort mirroring age and gender profile of the Czech population with an incident AD that entered the model.

The model

This microsimulation (i.e. patient-level) model has two branches: one branch represents the care usually provided (CAU) in the Czech Republic and the other a hypothetical case with timely treatment (TT). There are two main differences between the two branches of the model. First, as the purpose of the considered intervention is to ensure timely treatment, treatment is initiated in the TT branch when the cognitive deficit is mild. In the CAU branch, diagnosis only occurs when there is already a moderate cognitive deficit, which is a somewhat conservative assumption reflecting the Czech situation. Second, the probability of a patient being diagnosed and treated is higher in the TT branch than in the CAU (1 and 0.5,

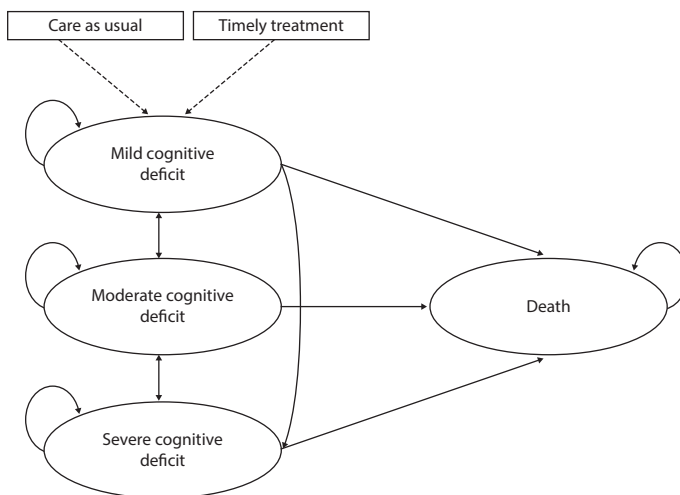
respectively). After accounting for mortality that occurs before diagnosis, two-thirds of people are diagnosed (timely) in the TT branch, and one-quarter of people are diagnosed (when they already have a moderate cognitive deficit) in the CAU branch of the model. The TT figure represents an ambitious but feasible goal (*Dementia Statistics Hub*, 2019), while the CAU figure is in line with the Czech estimates (Mátl, 2016).

Transitions among health states

Regardless of the branch, the patient migrates through four health states in discrete cycles lasting one year. The four states of this model are 'mild cognitive deficit' (MMSE 28 – 21), 'moderate cognitive deficit' (MMSE 20 – 11), 'severe cognitive deficit' (MMSE <11), and 'death' (see Figure 2). The transition between health states depends on the cognitive score of the patient in a given cycle as measured by the MMSE score. The backbone of the model are two established decline schemes representing the progression of the disease in an individual: the Mean decline scheme (Weimer – Sager, 2009) and a decline scheme defined by Lopez *et al.* (2005). The Mean decline scheme assumes that the annual decrease of the MMSE score is a random variable with a negative truncated normal distribution. The parameters of the Mean decline scheme differ for treated and untreated people, with the cognition of those who are treated declining slower. The decline scheme by Lopez assumes an annual decline expressed as a random variable with uniform distribution. This time the parameters differ according to a disease progression pace (slow and fast progressors), with the treated people having higher chance of slower progression than those who remain untreated. The parameters of both the Mean decline scheme and Lopez's decline scheme are summarised in Table 1. In the model, each patient has an equal chance (i.e. 50%) of declining according to the Mean scheme and Lopez's scheme.

Everyone enters the model untreated with an MMSE score of 28. The MMSE score in the current cycle is the annual cognitive decline as given by disease progression scheme subtracted from the score in the previous cycle. Cognition is tested every cycle and the new score determines whether the person has made any transition between health states

Figure 2 The structure of the model



Source: Author's illustration.

Table 1 Parameters of the decline schemes

Patient	Distribution	Distribution parameters	Unit
<i>Mean decline scheme</i>			
Untreated	truncated normal	(0, ∞); μ 3.5; σ 1.5	MMSE per year
Treated	truncated normal	(0, ∞); μ 1.5; σ 1.5	MMSE per year
<i>Lopez's decline scheme</i>			
Untreated fast	Uniform	(3, 6.8)	MMSE per year
Treated fast	Uniform	(3, 5)	MMSE per year
Untreated/treated slow	Uniform	(-1, 2)	MMSE per year

Source: Weimer and Sager 2009, authors' summary.

or has declined to a score when treatment is supposed to be initiated. The time of diagnosis is a random number from uniform distribution with an interval corresponding to moderate cognitive impairment for the CAU and mild cognitive impairment for the TT branch of the model.

Outcomes

The two main outcomes of this model are costs and quality of life (measured in quality-adjusted life years, QALYs). They are both discounted to the value of the year 2017 by a discount rate of 3% per annum. Four different cost categories are considered: the costs of 'informal care', 'timely diagnosis', costs of 'medication', and 'outpatient care'. While the costs of informal care

capture the burden of care usually provided by family caregivers, the other three categories jointly make up the costs of providing medical treatment (health-care costs). The costs of informal care are periodically incurred from the start of the model's run until the patient's death regardless of whether she has actually been diagnosed by a doctor. The costs of medication and outpatient care are periodically incurred by treated patients from the cycle in which treatment is initiated until their death. The costs of timely diagnosis are one-time costs incurred only by treated patients in the TT branch of the model in the cycle in which their treatment is initiated.

With the costs of informal care and medication being conditional on the patient's health state, there

are separate figures for mild, moderate, and severe cognitive deficit. These figures are based on Czech published research and a medical cost database (SUKL, 2015; Holmerová et al., 2017). Outpatient care consists of an identical series of medical checks regardless of the patient’s state of health (Mohelská et al., 2015). The costs of timely diagnosis were estimated by costing a series of diagnostic procedures used in a foreign study (Boustani et al., 2005) on the basis of reimbursements paid by Czech health insurers (General Health Insurance Fund, 2017). Specifically, a diagnostic scheme consisting of a visit to a general practitioner, visits to neurologists, a sampling of blood and cerebrospinal fluid, and – for only 5% of the individuals examined – an MRI or CT scan. According to Boustani et al. (2005), thirty-one people over the age of 65 need to be screened in order to diagnose one patient with AD. Consequently, the cost of timely diagnosis equals thirty-one times the costs of the described procedures per patient.

The quality of life enjoyed by a person with AD depends in a model cycle in each model cycle on the MMSE score. In particular, the patient’s QALY amounts to $0.408 + 0.01\text{MMSE} - 0.159\text{institutionalised} - 0.004\text{NPI} + 0.051\text{partner}$. These values are derived from a published regression equation (Jönsson et al. 2006). As in Barnett et al. (2014), the last three parts of the equation, *being institutionalised*, the

neuropsychiatric inventory instrument score, and whether the patient lives with a *partner-caregiver*, go beyond the level of detail of this model and are omitted here.

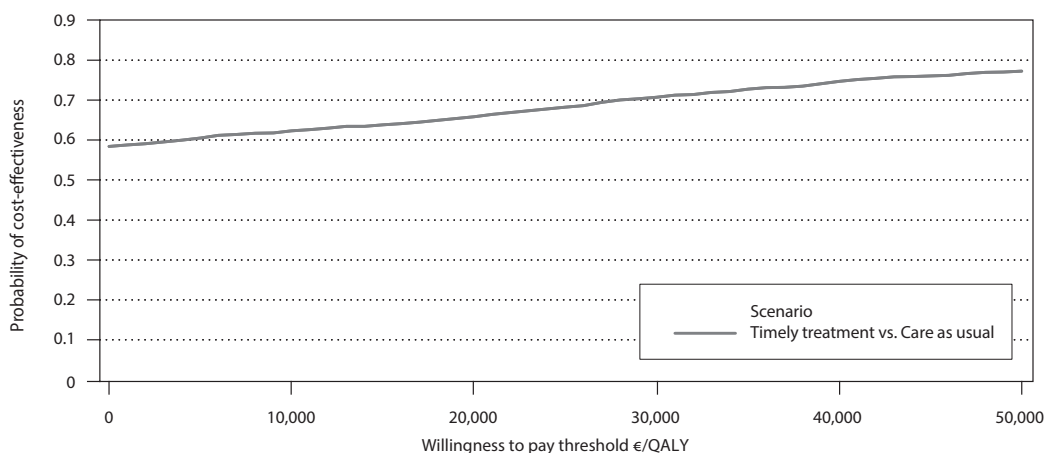
Sensitivity analyses

Parameters that may arguably have the biggest impact on the cost-effectiveness of the TT were chosen for the probabilistic sensitivity analyses (PSA) using the following distributions: the probability of being diagnosed and treated in the CAU branch (uniform (0.25; 1)), the MMSE scores at treatment initiation in the CAU branch (uniform (21; 28)) and the TT branch (uniform (21; 28)), and the costs of informal care (mild: gamma (0.86; 17,797), moderate: gamma (4.89; 5,212), severe: gamma (2.51; 12,092)). The results of the PSA are depicted using the cost-effectiveness acceptability curve (Briggs, 2000; Fenwick et al., 2001).

RESULTS

The results suggest that timely treatment of AD would represent a dominant strategy in the Czech Republic and would yield net benefit of EUR 13,751 per patient. The costs of the care usually administered have now reached EUR 122,430 per lifetime of an average patient, whereas the lifetime costs

Figure 3 Cost-effectiveness acceptability curve



Source: Author’s calculation.

of an average patient who receives timely treatment amount to EUR 117,380. In terms of health effects, TT was observed to slightly improved quality of life from 3.67 cumulative lifetime QALYs for an average patient to 3.87 QALYs. Consequently, intervention results in higher quality at a lower cost. The corresponding ICER is -26,121.

Both the decrease in lifetime costs and the increase in lifetime quality is achieved by shifting a part of the time spent in moderate and severe health states to time spent in mild and moderate health states, respectively. In numerical terms, an average patient lives 0.55 year longer with a mild cognitive deficit and 0.54 years longer with a moderate cognitive deficit when TT is implemented than if CAU is provided. The difference in costs comes from the savings on informal care on the one hand and the increase in healthcare costs on the other. The health-care category consists of three sub-categories: diagnosis, medication, and outpatient care. Diagnosis (screening) is the main driver of the increase in health-care costs per patient in the TT branch, accounting for EUR 2,776 of the total increase of EUR 3,616. Nevertheless, these additional health-care costs are outweighed by savings on informal care amounting to EUR 8,666 (121,742 - 113,076) per patient.

The outputs of the PSA are summarised in the cost-effectiveness acceptability curve in Figure 3. In 58% of a thousand repetitions, timely treatment is cost-effective even for the willingness to pay for QALY equal to EUR 0. The probability of an intervention being cost-effective further grows to 76% for the willingness to pay EUR 45,000, which is the standardly used threshold in the Czech Republic (SUKL, 2017).

DISCUSSION

Using a microsimulation model, we found that timely treatment would represent a dominant strategy in the Czech Republic. Our results are consistent with the findings of previous studies in the United States (Weimer - Sager, 2009) and United Kingdom (Getsios *et al.*, 2012). In the same vein, Handels *et al.* (2017) found that the use of biomarkers in the cerebrospinal fluid improves a patient's prognosis by 11% and results in an average QALY gain of 0.046 and EUR

432 additional costs per patient, with an ICER of EUR 9,400.

The subgroup analysis by Broulíková *et al.* (2018) illustrated the role of gender and age in the cost-effectiveness of timely treatment in the Czech Republic. Generally, women with disease onset at the age of 70 and 80 enjoy higher benefits than men because of their longer life expectancy, with a net benefit of up to EUR 25,969 for the average woman who gets AD at the age of 70. For disease onset at the age of 90, the net benefit is slightly higher for men because, according to the Czech life tables, from this point their life expectancy becomes higher than that of women of the same age. As expected, the net benefit decreases with the degree of cognitive deficit at the time of diagnosis and with the person's age at the time of the disease's onset. The former effect is given by the opportunity for people who receive timely treatment to retain their independence for a longer period of time. The latter effect again follows from a longer lifetime period during which patients can enjoy the effects of treatment; i.e. people who get the disease at a very old age likely die before declining to a severe stage of the disease regardless of treatment. The difference between CAU and TT thus diminishes with age. However, the results showed a positive net benefit for all subgroups except patients who are over the age of 90 and are diagnosed with an MMSE score below 23. Even in this case, the opportunity loss from indicating costly treatment is negligible and amounts to tens of euros per patient lifetime.

The present study has several limitations. First, although we innovatively derive the profile of the incident cohort of people get AD from the Nationwide Register of Hospitalised Patients, this source does omit people who were diagnosed and treated in outpatient care and were never hospitalised (for dementia or other diagnosis). Consequently, the age and gender composition of the Czech population living with AD might be biased. The solution to this problem in future research is to use the newly established National Register of Reimbursed Health Services, which also contains diagnoses made in outpatient care. This source might be used further to track the health-care consumption of people living with dementia and, thus, further improve the unit costs used in the model. Second, reliable data on the time

of diagnosis is missing. Our assumption regarding the current diagnostic timing in the phase of moderate cognitive impairment was rather conservative because available studies suggest that dementia is diagnosed late, usually shortly before death. However, more specific information is needed on the share of people who are diagnosed in the mild, moderate, and severe phase of the disease. Finally, dementia progression is better captured by a multidimensional progression scheme, such as the one recently suggested by Green *et al.* (2019).

This article provides an important contribution to the ongoing debate around dementia management in the Czech Republic. Our results generally support

the effort to increase access to a timely diagnosis and to post-diagnostic support, which has been declared as a priority in the National Action Plan for Alzheimer's Disease and Related Illness (*Ministry of Health of the Czech Republic*, 2021). Future research should overcome the limitations mentioned above by incorporating more country-specific data from the registers, but also, specifically, by evaluating the effect of the policies introduced by this government document. An example of such a policy is the cognition screenings provided in the office of general practitioners followed by referral to a specialist for those with suspected cognitive impairment.

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