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A preliminary economic evaluation of a potential program for the primary prevention of Alzheimer's disease

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ABSTRACT

Introduction: We evaluated the potential cost-effectiveness of a hypothetical primary prevention screening and treatment program to avert the biological and clinical onset of Alzheimer's disease (AD) in cognitively unimpaired older adults.
Methods: This hypothetical program would use an amyloid plaque-clearing antibody therapy monthly in the first six months and annually thereafter in cognitively unimpaired 55–79 year-old APOE4 carriers and 60–79 year-old non-carriers with a negative AD blood test (sensitivity and specificity of 0.9), averting the onset of moderately frequent neuritic amyloid plaques by 75 %. Lifetime hypothetical treatment outcomes were compared to natural history outcomes to estimate cost-effectiveness.
Results: The program would be cost-effective up to a per-dose price of $1173 in APOE4 carriers and $307 in non-carriers or a lifetime cost of $20,167 and $5146, respectively.
Discussion: Primary AD prevention could be cost-effective in older adults, especially in those at higher risk. Our findings and assumptions need to be confirmed with actual data.

1. Introduction

There is an urgent need to find and support access to Alzheimer's disease (AD) prevention therapies, which would be used in cognitively unimpaired individuals to partly or completely avert the onset of mild cognitive impairment (MCI) or dementia due to AD. "Secondary AD prevention therapies" (also known as "preclinical AD treatments") are those interventions that are used in cognitively unimpaired individuals with biomarker evidence of at least moderately frequent neuritic amyloid plaques (i.e., preclinical AD) to at least partly avert further biological, cognitive and clinical manifestations of AD, including the onset of cognitive impairment. "Primary prevention therapies" are those interventions that are used in cognitive unimpaired individuals without biomarker evidence of AD pathology to partly or even completely avert the biological, cognitive, and clinical manifestations of AD.

The amyloid plaque-clearing antibody therapies lecanemab [1] and donanemab [2] have been shown to slow cognitive and functional decline in individuals with mild cognitive impairment (MCI) and mild dementia to AD. These treatments and trontinemab, an investigational amyloid-targeting treatment, are now being evaluated in cognitively unimpaired individuals with biomarker evidence of preclinical AD, providing a chance to find and support the potential approval of the first secondary AD prevention therapy within 1–2 years. As we have recently noted in Reiman et al., [3] it may also be possible to conduct a primary prevention trial that finds and supports the approval of a subcutaneously and infrequently administered amyloid plaque-reducing therapy that is sufficiently safe and effective in averting the onset of the AD pathology within 4 years. Other treatment modalities might emerge as well.

Moving to primary prevention would follow the experience in other therapeutic areas, such as statin use to prevent cardiovascular events [4]. Aside from demonstrating treatment efficacy, an important consideration for preventative interventions is the economic viability of a screening and treatment program. The standard method to determine value for money of such prevention programs is cost-effectiveness analysis, which compares their incremental net cost, i.e., cost of screening tests and additional diagnostics, treatment, and monitoring less savings of medical and formal social care cost to gains in quality adjusted life-years (QALYs), i.e., the life-years gained from the treatment adjusted for quality of life in those years. Of note, the method does not seek to establish net cost savings but merely an acceptable cost-benefit ratio, which is conventionally up to $150,000 per QALY gained in the U.S.

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We recently suggested that a secondary AD prevention therapy might meet the criterion of adequate cost-effectiveness under a broad range of assumptions [5]. However, this finding cannot easily be extended to primary prevention, because the increase in time that will elapse until an adverse clinical event would occur and could be prevented means that fewer individuals will reach the adverse event in their lifetimes, even without treatment. Consequently, more individuals will need to be treated to avoid one event, which is referred to as Number Needed to Treat (NNT), mathematically the inverse of the absolute risk reduction. The larger NNT for primary prevention implies that many such programs, especially if including large parts of the population, are using scalable and low-cost interventions, such as childhood vaccinations and statins. However, complex interventions may also be used, if they can be targeted to high-risk populations, such as preventive mastectomy or oophorectomy to reduce risk of breast and ovarian cancer in BRCA-positive women [6].

Here, using a Markov model-based cost-effectiveness analysis framework, we explore whether and under which condition an intervention to prevent the development of AD pathology could generate adequate value for money. This hypothetical intervention would consist of blood biomarker testing of cognitively intact individuals to identify those who have not yet developed the pathology, treatment to avoid or delay its onset, and monitoring for progression to preclinical AD. We consider two scenarios, the first a risk-based approach that only includes APOE4 carriers [7] and the second a population-based approach without risk-based selection.

2. Methods

2.1. Description of hypothetical screening and prevention program

We assume that the program would target the 2026 U.S. population of ages 55 to 79, who are cognitively unimpaired, and project their lifetime outcomes under natural history and under an AD prevention program. In the first scenario, each individual would be tested for APOE4 carrier status and only included in the program if positive for either one or two alleles, which ~25 % of the population are [8], and in the second individuals, who are not APOE4 carriers, would be included, but the eligible age range narrowed to 60 to 79. Fig. 1 illustrates the identification of the eligible population and both scenarios. Population estimates and age-specific mortality rates were derived from U.S. Census data.

As shown in Fig. 1, each person (APOE4 carrier or non-carrier in their respective eligible age ranges) would receive a screening blood test for the AD pathology in primary care. The test would generate a positive, negative or indeterminate result with a sensitivity and specificity of 0.9 for the conclusive results based on the consensus recommendation from the Global CEO Initiative on Alzheimer's Disease [9]. Those with a positive result would be considered as having preclinical AD at baseline and treated accordingly but not considered in the model. Those with indeterminate test results (15 %) would be retested in the following year, and considered positive, if the results of the retest were indeterminate again or positive. Only individuals with conclusively negative screening test results, i.e., no evidence of AD pathology at baseline, would enter treatment and receive follow-ups. Individuals would receive a baseline MRI to screen for treatment contraindications, such as elevated risk of amyloid-related imaging abnormalities (ARIA) because of existing microhemorrhages, as required for all currently approved amyloid-targeting antibodies.

Treatment could be chronic, for example with six doses of an amyloid-targeting antibody in the first six months, followed by a single dose at month 12, and one dose annually thereafter, which we use as the base case. Another approach could be durable treatment, such as with active immunotherapy that may last several years. Follow-up would consist of one MRI after the first dose and biannual blood tests. Treatment for primary prevention would continue as long as the blood test remained negative. Individuals with false positive test results would incur treatment cost without benefit from the treatment and their costs are tracked in the model to accurately reflect the overall program cost. Individuals with indeterminate blood test results during follow-up are retested the following year; if the test remains indeterminate or turns positive, they are considered to have progressed to preclinical AD, and would no longer be considered for primary prevention treatment. While they could proceed to a treatment for preclinical AD, we are not considering this aspect and follow the natural disease history of those individuals over their lifespans, from development of preclinical and progression to prodromal AD and dementia due to AD with increasing severity, in order to isolate the value of primary prevention. Our base case assumption is that the treatment would decrease the incidence of AD pathology development by 75 %. This hypothetical estimate accounts for factors that reduce the treatment effect under real-world conditions such as treatment interruptions and discontinuations. Fig. 2

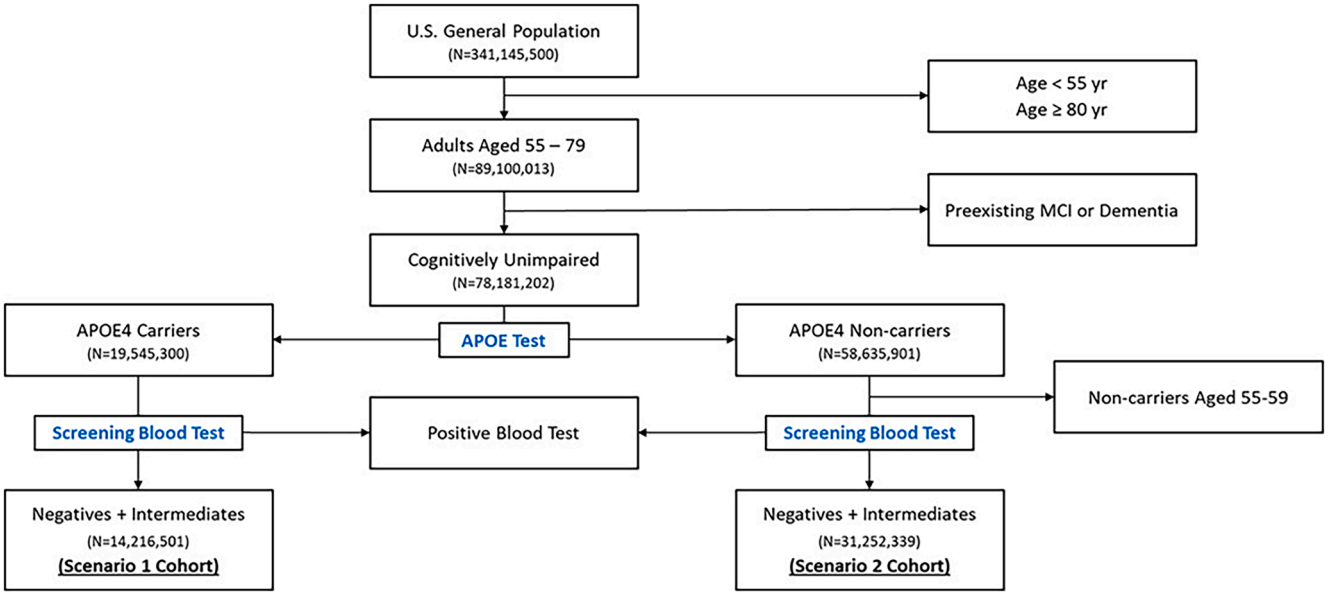

Fig. 1. Selection process of the eligible population.

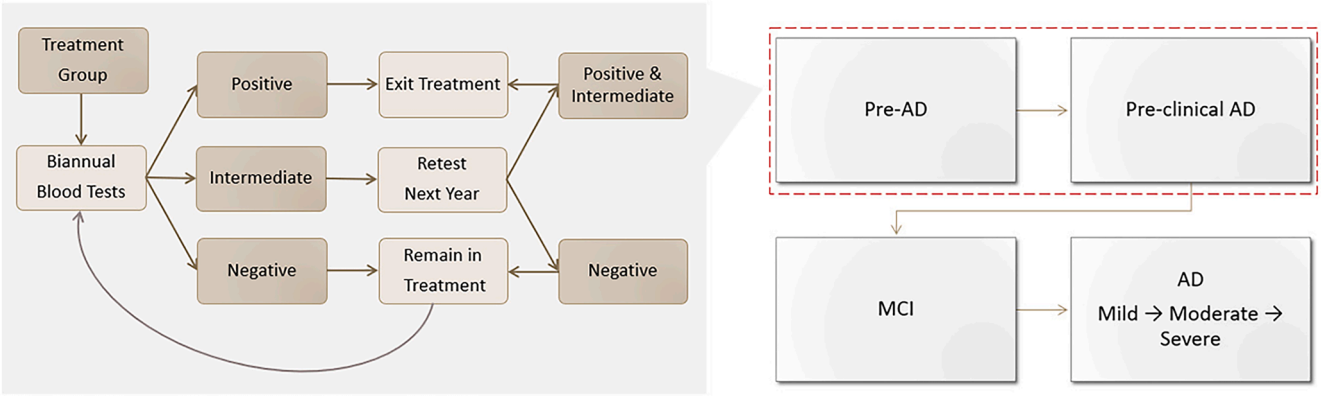

Fig. 2. Schematic representation of the model.

depicts the model schematic.

2.2. Model parameters

2.2.1. Disease risk and transition probabilities

As mentioned earlier, we are analyzing two different primary prevention programs, the first targeting APOE4 carriers, who are around 25 % of the population, and the second including the lower risk population of APOE4 non-carriers. We removed from the age-eligible population first those with prevalent MCI or dementia based on data from Petersen et al. [10] and Hebert et al., ([11], respectively. A 2022 publication by Jansen et al. [12] served as source for prevalence of preclinical AD among APOE4 carriers and non-carriers, i.e., cognitively intact individuals with biomarker evidence of the AD pathology who would be no longer eligible for a primary prevention program.

This publication also allowed us to estimate the annual transition probabilities to preclinical AD for both populations, as described in an earlier publication [5], and we calculated the progression rates separately for APOE4 carriers and the full population. Subsequent transition probabilities from preclinical AD to MCI were obtained from a 2019 meta-analysis by Parnetti et al. [13] and recent studies by Cho et al. [14] and Roberts et al. [15]. (Table 1)

2.2.2. Costs

We assumed the cost of an APOE test to be $141 and of a brain MRI without contrast $234 based on Medicare billing rates and cost of a blood test for the AD pathology to be $130. While the analysis was agnostic to the type of treatment, the base case assumed a hypothetical treatment cost of $1000 per dose, in addition to the cost of infusion delivery. (Table 2) We also estimated the average lifetime treatment cost. All costs were expressed in 2026 USD and discounted annually by 3 %.

2.2.3. Benefits

Benefits in the form of avoided medical and formal social care cost as well as individuals' QALY gains were considered through progression and death as the difference between the natural history of the disease and the trajectory under treatment because of the delay in onset of preclinical AD and subsequently MCI due to AD. Of note, differences only materialize after onset of MCI due to AD. We used two perspectives on value, the first being the payer perspective that includes direct medical and formal social care cost as well as gain in individuals' QALYs, and the second the societal perspective that also considers reduction in medical cost and time and productivity loss of caregivers as well as their QALY losses. Those benefits were discounted by 3 % annually as well.

Table 1
Model transition probabilities and baseline prevalence estimates.

Age Group	55–59	60–64	65–69	70–74	75–79	80–84	85+
Transition Probabilities							
No AD -> Pre-clinical AD	0.007	0.007	0.008	0.009	0.010	0.010	0.010
Pre-clinical AD -> MCI	0.010	0.015	0.015	0.024	0.026	0.026	0.026
MCI -> Mild AD	0.187	0.187	0.187	0.187	0.187	0.187	0.187
Mild AD -> Moderate AD	0.323	0.323	0.323	0.323	0.323	0.323	0.323
Mild AD -> Severe AD	0.044	0.044	0.044	0.044	0.044	0.044	0.044
Moderate AD -> Severe AD	0.401	0.401	0.401	0.401	0.401	0.401	0.401
Mild AD -> Nursing Home	0.038	0.038	0.038	0.038	0.038	0.038	0.038
Moderate AD -> Nursing Home	0.110	0.110	0.110	0.110	0.110	0.110	0.110
Severe AD -> Nursing Home	0.259	0.259	0.259	0.259	0.259	0.259	0.259
Male Mortality							
Mortality, MCI	0.016	0.023	0.031	0.045	0.070	0.115	0.237
Mortality, Mild AD	0.026	0.033	0.050	0.064	0.113	0.157	0.280
Mortality, Moderate AD	0.059	0.066	0.099	0.113	0.219	0.264	0.386
Mortality, Severe AD	0.205	0.212	0.260	0.274	0.452	0.497	0.619
Female Mortality							
Mortality, MCI	0.010	0.014	0.020	0.031	0.050	0.086	0.210
Mortality, Mild AD	0.016	0.020	0.030	0.041	0.074	0.110	0.235
Mortality, Moderate AD	0.034	0.038	0.057	0.068	0.133	0.169	0.294
Mortality, Severe AD	0.128	0.132	0.162	0.173	0.288	0.323	0.448
Prevalence							
Pre-clinical AD	0.180	0.210	0.250	N/A	N/A	N/A	N/A
MCI	0.044	0.067	0.084	N/A	N/A	N/A	N/A
Dementia	0.007	0.007	0.040	N/A	N/A	N/A	N/A

Note: Mortality risk in the pre-AD and preclinical AD stages would be that of the general population.

Table 2
Parameters for costs and benefits.

	MCI	Mild AD	Moderate AD	Severe AD
Treatment (per dose)	$1000			
Infusion	$150			
Blood Test	$130			
MRI	$233			
APOE Test	$141			
Annual Medical Care	$16,982	$19,921	$21,863	$22,496
Annual Social Care, Community	$2650	$4903	$5290	$7355
Annual Social Care, Nursing Home	$0*	$132,803	$132,803	$136,674
Caregiver Burden	$23,685	$40,369	$43,598	$49,042
Patient Utility	0.73	0.64	0.39	0.24
Caregiver Utility, Community	0.88	0.87	0.86	0.86
Caregiver Utility, Nursing Home	N/A	0.89	0.89	0.88

*We assume no admissions to nursing homes in the MCI stage.

2.2.4. Sensitivity analyses

To assess the robustness of the base case ICER findings, one-way sensitivity analyses were conducted. In these analyses, each input parameter was varied individually while holding all other parameters constant at their base values. All parameters were varied within the range of 50 % to 150 % of their base-case estimates to reflect uncertainty in clinical effectiveness, resource use, and cost inputs, with the restriction that the range was bounded by 0 and 1 for probability inputs. The parameters with the greatest influence on the ICER were identified and subsequently used in a threshold analysis, in which the values required for each parameter to achieve cost-effectiveness were calculated, both individually and in combination.

3. Results

3.1. Base case results

Table 3 summarizes the base case results. From a payer perspective, screening and treating APOE4 carriers would cost $26,352 per individual in overall average lifetime cost. The cost of the treatment would be responsible for four-fifths of the total costs (79.1 % for APOE4 carriers and 80.8 % for non-carriers) and cost of infusion delivery for around 12 %, whereas all other components of the prevention program would only account for around 2 to 3 % each. Put differently, lifetime program cost would decline to $23,290 for a treatment that does not require infusion delivery. APOE4 carriers would remain on treatment for an average of 15 years, and NNT to prevent one additional case of MCI was 21.7. By delaying progression into MCI and dementia and thus shortening the lifetime course of AD among APOE4 carriers, the treatment would save $18,296 in care cost and generate a gain of 0.14 QALYs per individual. Due to their higher average age and associated mortality, non-carriers would remain on treatment for an average of 14 years, with a NNT of 55.8 to prevent one additional case of MCI. The treatment would yield cost savings of $19,444 and generate a gain of 0.05 QALYs per individual for non-carriers.

Assuming a cost-effectiveness threshold of $150,000 per QALY gained, the risk-based approach of treating only APOE4 carriers would be considered cost-effective, with an incremental cost-effectiveness ratio (ICER) of $129,008 per QALY gained. This corresponds to an incremental net monetary benefit (INMB) of $2977 per individual from the payer perspective. In contrast, from the societal perspective, treating APOE4 carriers would yield an ICER of $100,767 per QALY gained and an INMB of $3774 per individual. Giving treatment to the lower- risk population of non-carriers would imply a slightly lower lifetime cost of $24,693 per individual but would not be cost-effective from either payer perspective ($371,453 per QALY gained) or societal perspective ($324,434 per QALY gained).

Table 3
Per-individual model results from payer perspective.

	Scenario 1: APOE4 Carriers		Scenario 2: Non-APOE4 Carriers	
	Treatment Group	Natural History Group	Treatment Group	Natural History Group
Total Costs	$26,352	$8056	$24,693	$5250
Treatment Cost	$17,190	N/A	$16,738	N/A
Average Length of Treatment	15 Years	N/A	14.2 Years	N/A
Infusion Cost	$2573	N/A	$2505	N/A
Blood Test Cost	$731	N/A	$641	N/A
MRI Cost	$467	N/A	$467	N/A
APOE Test Cost	$776	N/A	$353	N/A
Cost of Care	$4615	$8056	$3989	$5250
Saving on Care Cost	$3441	N/A	$1260	N/A
NNT	21.7	N/A	55.8	N/A
QALY Benefit	14.6 QALY	14.5 QALY	13.6 QALY	13.5 QALY
Incremental Cost	$18,296	N/A	$19,444	N/A
Incremental QALY Benefit	0.14 QALY	N/A	0.05 QALY	N/A
ICER (per QALY)	$129,008	N/A	$371,453	N/A
INMB	$2977	N/A	-$11,592	N/A

*Based on a valuation of $150,000 per QALY gained.
NNT, number needed to treat; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit.

3.2. Univariate sensitivity analyses

Fig. 3 illustrates the effect of varying one input parameter at a time on the predicted ICER for the 10 most influential parameters. The grey line between the orange and blue bars signifies the base case estimate of $129,008 per QALY gained for APOE4 carriers. The orange and blue bars illustrated how varying a parameter as described above would decrease or increase, respectively, the estimated incremental cost per QALY gained. The results suggest that the ICER was mainly sensitive to treatment price and effect size of the treatment in reducing the incidence of AD pathology. Test specificity appeared as a sensitive parameter in univariate sensitivity analyses. However, as it is generally well-established for diagnostic tests and is not considered a major driver of uncertainty in real-world applications, it was not included in the subsequent threshold analyses, which prioritized variable pairs more directly linked to decision uncertainty. As expected for an intervention with long latency to affect clinical outcomes, the predictions are sensitive to the assumed discount rate.

3.3. Threshold analyses

Tables 4 and 5 present two-way sensitivity analyses exploring the interaction between treatment price and treatment effect size, as the two parameters with the largest effect on the ICER prediction based on the univariate sensitivity analysis. In the base case, assuming a constant treatment effect size of 75 %, the cost-effective threshold price from the payer perspective was $1173, corresponding to a lifetime treatment cost threshold of $20,167 for an infusion treatment and $17,750 for a non-infusion treatment. If the treatment effect size were reduced by nearly half to 35 %, the cost-effective threshold price would decrease by more than 60 % to $389, lowering the lifetime treatment cost threshold to $6532. Conversely, if the treatment were highly effective, with an effect size of 95 %, the threshold price and lifetime treatment cost would rise to $1579 and $27,475, respectively. When non-APOE4 carriers were treated, the threshold price declined to $307, with a corresponding lifetime treatment cost of $5146. From the societal perspective, the cost-effective threshold price was $1439 when treating APOE4 carriers and

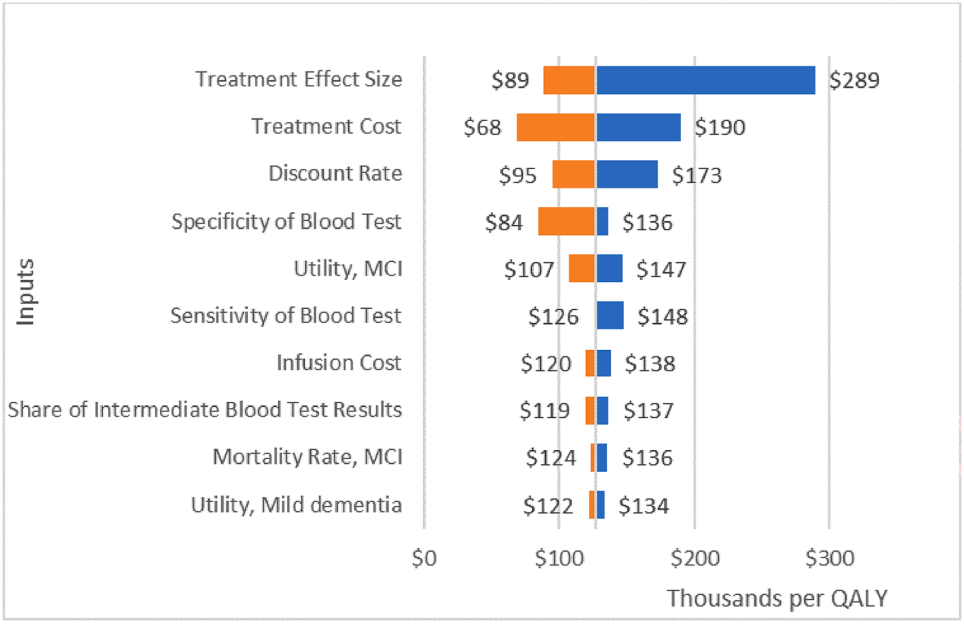

Fig. 3. Results from univariate sensitivity analysis.

Table 4
Two-way sensitivity analysis of incremental cost-effectiveness ratio from payer perspective, scenario 1: APOE4 carriers.

		Lifetime Treatment Cost per Patient								
		$1,074	$2,149	$4,298	$8,595	**$17,190**	$25,785	$38,678	$58,017	$87,026
		Treatment Cost per Dose								
		$63	$125	$250	$500	**$1,000**	$1,500	$2,250	$3,375	$5,063
	35%	$63,214	$79,827	$113,054	$179,507	$312,414	$445,320	$644,680	$943,719	$1,392,279
	45%	$43,276	$56,123	$81,819	$133,209	$235,989	$338,770	$492,941	$724,197	$1,071,081
	55%	$30,590	$41,042	$61,944	$103,749	$187,358	$270,968	$396,382	$584,504	$866,686
Effect Size	65%	$21,810	$30,603	$48,187	$83,356	$153,693	$224,031	$329,537	$487,797	$725,186
	75%	$15,373	$22,949	$38,100	$68,403	**$129,008**	$189,612	$280,520	$416,880	$621,422
	85%	$10,453	$17,098	$30,389	$56,970	$110,132	$163,294	$243,038	$362,653	$542,075
	95%	$6,570	$12,481	$24,302	$47,946	$95,232	$142,519	$213,449	$319,844	$479,436

The line in between cells indicates the threshold of cost-effective ICERs.

Table 5
Two-way sensitivity analysis of incremental cost-effectiveness ratio from payer perspective, scenario 2: APOE4 non-carriers.

		Lifetime Treatment Cost per Patient								
		$1,046	$2,092	$4,184	$8,369	**$16,738**	$25,107	$37,660	$56,490	$84,735
		Treatment Cost per Dose								
		$63	$125	$250	$500	**$1,000**	$1,500	$2,250	$3,375	$5,063
	35%	$183,404	$226,621	$313,055	$485,924	$831,660	$1,177,396	$1,696,001	$2,473,908	$3,640,768
	45%	$136,852	$170,389	$237,463	$371,610	$639,905	$908,201	$1,310,643	$1,914,307	$2,819,803
	55%	$107,229	$134,606	$189,359	$298,866	$517,881	$736,895	$1,065,416	$1,558,198	$2,297,371
Effect size	65%	$86,721	$109,834	$156,058	$248,506	$433,403	$618,299	$895,644	$1,311,661	$1,935,688
	75%	$71,683	$91,668	$131,637	$211,576	**$371,453**	$531,330	$771,145	$1,130,868	$1,670,453
	85%	$60,184	$77,777	$112,963	$183,335	$324,080	$464,824	$675,940	$992,615	$1,467,627
	95%	$51,106	$66,811	$98,221	$161,041	$286,680	$412,320	$600,779	$883,468	$1,307,501

The line in between cells indicates the threshold of cost-effective ICERs.

$409 when treating non-carriers, translating to lifetime treatment costs of $24,739 and $7039, respectively.

4. Discussion

This study is, to our knowledge, the first exploratory economic analysis of a hypothetical screening and primary prevention program for AD in the U.S. The results suggest that such a program could meet

standard thresholds for cost-effectiveness over a wide range of assumptions for treatment cost and effect size in APOE4 carriers, who have an elevated risk of developing the disease. The program could even be cost-effective for the lower-risk APOE4 non-carriers, albeit in a much narrower range. Assuming an effect size of 75 %, the maximum cost-effective lifetime treatment cost would be around $20,000 for APOE4 carriers and around $5000 for non-carriers. Similarly, at our base case assumption of $1000 per dose, the treatment would remain cost-effective with an effect size of 66 % in carriers, whereas not even complete elimination of the progression to preclinical AD would be cost-effective in non-carriers. It is also important to note that the cost of the treatment accounts for around 80 % of program cost, implying that other components, such as blood tests and MRIs, play a minor role in such economic considerations.

A previous study evaluated the cost-effectiveness of a hypothetical treatment that reduces progression from preclinical AD to early-stage clinical AD [5]. As expected, the cost-effective threshold for treatment cost in this secondary prevention was considerably higher than our estimates for primary prevention, with a lifetime cost of $60,000 and an effect size of reducing risk of progression to MCI due to AD by 50 %, even in an unselected population. Value could even be increased further by targeting high-risk individuals, such as those with high p-tau 217 levels, because of their higher baseline risk of progression [16]. That difference stems from the fact that the value of AD prevention reflects the lifetime effects of delayed or avoided onset of MCI due to AD. Moving earlier in the disease process means that more individuals have to be treated to avoid one such case of progression, with a NNT of 13 for preclinical AD [5], 22 for primary prevention in APOE4 carriers and 56 for non-carriers.

The findings illustrate that preventive treatments, which are usually assumed to have low per-individual cost, such as statins with annual cost of $180–360 [17], can be cost-effective at fairly high cost. While the attributable cost of caring for manifest AD are modest [18], the limited effect of the disease on near-term mortality implies that those costs accrue over a long period of time. Thus, preventing rather than treating manifest AD creates much greater economic value. Another important consideration is that the diagnostic and treatment process in early-stage AD is very complex and relies heavily on specialty care, an approach that is not scalable for this a population-level disease given the limited capacity of those specialists [19].

As stated earlier, the first secondary AD prevention therapy could be proven effective within the next 2 years, and it may even be possible to support approval of the first effective primary prevention therapy within the next 4 years [3]. However, trialing the effectiveness of amyloid-targeting treatment in secondary prevention should not be a precondition for investigating whether these or other treatments will be effective in primary prevention. While now being considered, a primary prevention trial of a plaque-reducing antibody therapy that is administered subcutaneously and hence more accessible than an intravenously administered therapy [20], has not yet started. More work is also needed using the latest generation of blood tests in large population-based studies to support their use in screening programs.

Universal access to such prevention programs requires coverage by health insurance. It remains uncertain whether future clinical trial results will be compelling enough to secure insurance reimbursement for these programs. Nevertheless, assuming that the efficacy of primary prevention programs is supported by future trials, two additional challenges in the U.S. are that Medicare does not cover preventive treatments statutorily and private payers might balk at incurring the cost because of the delayed accrual of benefits, and both could be resolved with a positive recommendation of the U.S. Preventive Services Task Force. Thus, it will be important to generate the data needed to show the value the screening blood test, and subsequent treatments informed by their results—and to communicate the data, even before the first trials are completed.

4.1. Limitations

The study needs to be understood in the context of its limitations. First and foremost, it is an exploratory economic evaluation using the cost-effectiveness framework relying on assumptions rather than empirical data for many parameters. An actual cost-effectiveness study would require data on the exact nature of the clinical pathway, route of administration route, frequency, cost and accuracy of blood tests, eligibility criteria and cost and effect size of the treatment. We assume that the treatment effect is homogenous for all age groups and both sexes and disregard the effect of etiologies other than AD on development and progression of cognitive impairment as well as effect of comorbidities.

5. Conclusion

We conducted a thought experiment within the framework of cost-effectiveness analysis to explore the economic viability of a primary prevention program. The results suggest that a primary prevention program for AD might meet conventional criteria for cost-effectiveness in high-risk groups, such as APOE4 carriers, and potentially even in lower-risk groups depending on treatment cost. Given the complexity of implementing such as program, it is our hope that those results inform discussions about implementation as well as affordability and access well ahead of these treatments becoming available.

Consent statement

As the study did not constitute human subjects research per U.S. federal regulations (45 CFR 46, 102(f))20, it was exempt from IRB review, consent requirements and registration.

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CRediT authorship contribution statement

Soeren Mattke: Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Jiahe Chen:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis. **Eric M Reiman:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

Outside of the submitted work USC has research agreements, on which Dr. Mattke is PI, with Alzheon, Biogen, C2N, Eisai, Lilly and Roche/Genentech. SM serves on the board of directors of Senscio Systems, Inc., and the scientific advisory board of AlzPath and Boston Millennia Partners. He has received consulting and/or speaker fees from Biogen, C2N, Eisai, Eli Lilly, Novartis, Novo Nordisk and Roche/Genentech. Dr. Reiman is a leader in Banner Alzheimer's Institute's Alzheimer's Prevention Initiative (API), which includes public-private partnerships and collaborations in the evaluation of investigational Alzheimer's prevention therapies. API uses Lilly and philanthropic support for its collaboration with Lilly in Trailblazer-ALZ 3, a secondary prevention trial of donezemab, philanthropic support for its collaborative role with Lilly in Trailrunner-ALZ 3, a secondary prevention/early prevention trial of remternetug, philanthropic support for its collaborative role with Lilly in a potential primary prevention trial, and NIH, NOMIS Foundation, Lilly and Roche support for the next API Autosomal Dominant AD Colombia Prevention Program. He is a is a co-founder,

advisor and shareholder in ALZpath, which has a pTau217 capture antibody that is being used to assess plasma pTau217 levels on several commercial and research immunoassay platforms that could be used in the screening of potential prevention therapies. He is a compensated scientific advisor to Alzheon, Cognition Therapeutics, Denali, Enigma, Jocasta Neuroscience, Retromer Therapeutics. and Vaxxinity. Mr. Chen reports no conflicts.

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