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A Cost-Consequence Analysis of Different Screening Procedures in Alzheimer's Disease: Results from the MOPEAD Project

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Abstract.
Background: For care planning and support, under-detection and late diagnosis of Alzheimer's disease (AD) is a great challenge. Models of Patient-Engagement for Alzheimer's Disease (MOPEAD) is an EU-funded project aiming at testing different strategies to improve this situation.
Objective: To make a cost-consequence analysis of MOPEAD.
Methods: Four screening strategies were tested in five countries (Germany, the Netherlands, Slovenia, Spain, and Sweden): 1) a web-approach; 2) Open-House initiative; 3) in primary care; and 4) by diabetes specialists. Persons-at-risk of AD in all strategies were offered referral to a hospital-based specialist. The primary health-economic outcome was the cost per true-positive case (TP) of AD from the screened population.
Results: Of 2,847 screened persons, 1,121 screened positive (39%), 402 were evaluated at memory clinics (14%), and 236 got an AD diagnosis (8%). The cost per TP of those screened was €3,115 with the web-approach, €2,722 with the Open-House, €1,530 in primary care, and €1,190 by diabetes specialists. Sensitivity analyses that more likely reflect the real-world situation confirmed the results. The number-needed-to-screen was 30 with the web-approach, 8 with the Open-House and primary care, and 6 with the diabetes specialists.
There were country differences in terms of screening rates, referrals to memory clinics, staff-types involved, and costs per TP.
Conclusion: In primary care and by the diabetes specialist, the costs per TP/screened population were lowest, but the capacity of such settings to identify cases with AD-risk must be discussed. Hence new diagnostic strategies such as web-solutions and Open-House initiatives may be valuable after modifications.

Keywords: Alzheimer's disease, cost-consequence analysis, cost analysis, costs, dementia, diagnosis, diagnostic work-up, screening

INTRODUCTION

In 2015, Prince et al. suggested that dementia would affect about 50 million people worldwide today [1]. Due to dramatic demographic changes of an overall increasing population age and a higher proportion of older people, this number will increase over the next decades to over 130 million by 2050 [1].

The estimated worldwide costs of dementia were estimated at US$818 bn in 2015, an increase of 35% since 2010 [2]. The economic and social costs could pose a threat to public health, to an extent that has led the World Health Organization to declare dementia control a global health priority [3].

This requires cost-effective, innovative solutions such as development of tools for preventing or reducing the incidence, severity, and economic burden of dementia, of which Alzheimer's disease (AD) accounts for 60–80% of all cases [4]. Currently, a significant proportion of AD dementia cases remain undiagnosed or receive a late-stage diagnosis [5–8]. It is unclear what the best ways are for detecting these undiagnosed cases and how much effort that would take.

The European Union Innovative Medicines Initiative project, Models of Patient Engagement for Alzheimer's Disease (MOPEAD), aims to improve early detection of AD. The screening goal is to identify undiagnosed people at high risk of AD in different settings in different European countries.

MATERIALS AND METHODS

Study design

We analyze in a prospective study the costs and consequences of four strategies for early detection of AD across five European countries. A detailed description of the project has been published by Rodríguez-Gómez et al. [9].

MOPEAD has an explorative and implementation research nature [10]. Thus, the analyses are based on the principle of cost-consequence analysis [11]. This type of analysis presents relevant costs and effects (consequences) to capture as much information as feasible, to allow decision makers to get a broad overview of the economic analyses.

Since countries differ in terms of how care is organized and financed, as well as different cultural aspects, both overall and country specific results were analyzed.

Screening procedures

A set of four multi-country, multi-center strategies (in MOPEAD labelled "Runs") were implemented, targeting people between 65 and 85 years of age for AD-diagnostic work-ups:

Run 1 is an AD Citizen Science tool with a web-based approach. With online marketing methods, individuals are invited and agree to have data collected and used for scientific purposes [9].

Run 2: Open House Initiative, where individuals, after marketing methods, are invited to memory/specialist clinics [9].

Run 3: Primary Care Campaign, where patients on regular visits to primary care are invited [9].

Run 4: Type 2 diabetes campaign, where patients on regular visits for Type 2 diabetes are invited [9].

From these four runs, a subset of positively pre-screened patients was offered referral to memory clinics for a full diagnostic evaluation (work package 3, WP3), including a medical examination, blood tests, neuropsychological testing, magnetic resonance imaging (MRI), and optional cerebrospinal fluid (CSF) analyses. The goal was to perform 2,000 screenings (100 screenings per run across the five countries) and to evaluate 660 persons at the hospital-based specialist level (33 per run across the five countries). Scales are summarized in Supplementary Table 1.

The full diagnostic work-up at memory clinics (WP3) served as the "gold standard" to confirm or reject the diagnosis of AD of the pre-screened positives. Naturally, in this design, we do not have any clinical work-up data of those that screened negative. Therefore, no estimates of the proportion of false negatives will be available.

Outcomes

All costs are expressed as €2019. The country-specific staff resources and unit costs for Runs 2–4 and the full diagnostic at memory clinics (WP3) can be seen in Supplementary Tables 2–4 (hourly rates, overhead costs), and Supplementary Tables 9–11 (staff time, use of diagnostic tools). For Runs 2–4, the major cost drivers are staffing costs. As seen for the non-staff costs, there is variability in costs for advertisements, rents, parking, transportation, etc., which is adjusted in the sensitivity analysis S3 (see below). The results are described both as aggregated (main text) and on the country level (Supplementary Tables 5–8, 12–15).

The primary health-economic outcome is the comparison of the cost per true positive (TP) case of AD dementia and mild cognitive impairment (MCI) due to AD from the whole population screened in each run (labeled as AD).

Secondary health economic outcomes are: a) comparisons of the cost per TP case of AD from the population with a positive screening in WP2 in each run; b) comparisons of the cost per TP case of AD of those who entered the full diagnostic at memory clinics (WP3) and got a final diagnosis of AD-dementia in each run.

A set of non-monetary outcomes from each Run is also presented, such as:

- The number of screenings and referrals to the full diagnostic at memory clinics (WP3) from the population of all persons screened.
- The number of positive screenings from the population of all persons screened.
- The number needed to screen to identify one TP of MCI or mild dementia due to AD.

Sensitivity analysis

There are difficulties to separate project-driven costs and effects, as well as to predict what the results had been in "real world" in the different runs. Thus, the results of the cost-consequence analysis are presented in two ways: the within project costs and consequences (base case), and in a set of sensitivity analyses to try to adjust inputs to better reflect "real world".

For the sensitivity analysis of Runs 2–4, the following four approaches were used:

S1. The unit costs for salaries varied substantially in the different countries in Runs 2–4. In some countries, staff were paid extra to do the work as the work was done outside regular working time, while in other countries, additional staff was used, etc. Therefore, in this approach, a uniform source for staff salaries (http://www.salaryexplorer.com, see Supplementary Table 4) was used to get country-specific costs for similar staff-types. Furthermore, the registered time for the staff type "other staff" varied between countries. Therefore, in S1, this staff-type was excluded (but included in S3). In the base case, the costs for the use of licensed scales varied due to local agreements in some countries. Therefore, in S1, the costs for the scales are harmonized.

S2. Similar as S1. However, since the use of staff-types varied (e.g., nurses versus physicians), in S2, it was assumed that the hourly rates for staff was the average from the health sector in each country (same source as above in S1).

S3. In some countries, very detailed information was given for rent of facilities, travel costs, administrative time, "other staff" (see above), etc. In S3, it is assumed that all countries in Runs 2–4 include these detailed costs (added after GDP/capita adjustment) when data is missing from a country. Salaries are harmonized as in S1 (which may lower salary costs as compared to the base case).

S4. The management of uncertainty in Run 1 is somewhat different from Runs 2–4 since it is a web application. The challenge is to put a price for the use of the application. In MOPEAD, there was a special discount for the project. We have now included two other prices for the use of the application: the first is zero (0), the second is the price without the discount.

Run 1 also differs from Runs 2–4 since no face-to-face meeting takes place. Thus, the study population in Run 1 is difficult to characterize, but the number of TPs will probably be lower than in Runs 2–4. Therefore, we also test a scenario with a hypothetical change in the cut off that might double the proportion of TPs, also resulting in a halved number needed to screen.

S5. In some countries and runs, there were no TPs at the full diagnostic at memory clinics (WP3): Germany in Run 1 and Sweden and the Netherlands in Run 4. These countries are "high-cost countries" as compared to Slovenia and Spain, which might impact the results and a situation with no TPs hardly represents "real world". Thus, in S5 we tested two imputation approaches of TPs for countries reporting zero TPs: mean TPs from the other countries in Runs 1 and 4 respectively and a TP of 1 instead of zero.

Statistical analyses

For the different runs, mean values of costs in relation to different outcomes were used. Resource use and costs in care are often skewed, so in regression analyses in health economics, gamma distributions with log-links are frequently used. Thus, a generalized linear model (GLM) was applied where the cost per TP was the dependent variable with age, gender, Mini-Mental State Examination (MMSE), run, and country as background variables (Supplementary Table 13).

RESULTS

Screening rates

Runs 1–2 exceeded the screening goal while Runs 3–4 did not reach the goal (Table 1). The proportion of positive screens varied between 35–58%. Run 1 screened the greatest number of people but had also the lowest attendance rate to the full diagnostic at memory clinics (WP3), and the lowest proportion of TPs. The NNS (number-needed-to-screen) to identify a TP varied between 6 (Run 4) to 30 (Run 1). Although the positive screen proportion in Run 1 was similar to that in Run 2, the number of attendees at WP3 was low (6% of screened), as well as the ending number of TPs in relation to the screened population (3%).

The country-specific results for the different runs are seen in Supplementary Tables 5–15.

In Run 1 (Supplementary Table 5), Slovenia and Spain screened the most persons. The proportion of TP of those screened varied between countries (0–30%). In Slovenia there was a gap between those who screened positive and those who were contacted. Because of expected capacity problems, there was a

Table 1
All countries: study populations outcomes

ALL countries	RUN 1 The web	RUN 2 Open House	RUN 3 Primary care	RUN 4 Diabetes specialist	All
Numbers					
Completed screenings	1,487	661	435	264	2,847
Positive screen	547	230	191	153	1,121
Invited to WP3 (specialist)	477	218	188	150	1,033
Contacted for referral to WP3	174	214	179	143	710
Evaluated at WP3	91	161	94	56	402
TP at WP3	49	82	58	47	236
Proportions (%)					
Positive screens of screened	37%	35%	44%	58%	39%
Invited of screened positive	87%	95%	98%	98%	92%
Contacted of screened positive	32%	93%	94%	93%	63%
WP3 of screened	6%	24%	22%	21%	14%
WP3 of positive screens	17%	70%	49%	37%	36%
TP of contacted	28%	38%	32%	33%	33%
TP of positive screens	9%	36%	30%	31%	21%
TP of evaluated	54%	51%	62%	84%	59%
TP of screened	3%	12%	13%	18%	8%
NNS/TP	30	8	8	6	12

TP, true positive with confirmed diagnosis of MCI or mild dementia due to AD at WP3; NNS, number needed to screen.

decision that resulted in a referral to general practitioners for further diagnostics instead of referral to the full diagnostic at memory clinics (WP3) for 70 persons who screened positive. Also, in Run 2 (Supplementary Table 6), there was great variability in the TPs of screened. The very high NNS/TP in the Netherlands depends on the fact that only 1 TP was identified. The highest attendance rate to WP3 of those who screened positive was in Run 2 (70%). In Run 3 (Supplementary Table 7), 50% of those that screened positive visited WP3, with similar figures for the different countries, except Germany. In Sweden, Slovenia, and Spain, the TP proportions were similar. The high NNS/TP in Germany is because only one TP was identified. In Run 4 (Supplementary Table 8), Slovenia and Spain had a high recruitment rate, while it was much lower in Sweden, Germany, and the Netherlands. In Sweden and Germany, no TPs were identified, while the TP proportions were high in Slovenia and Spain.

Resource use

The greatest use of time occurred in Runs 2 and 4 (Supplementary Table 9). The different types of staff that were involved also varied between countries and runs. Particularly in Sweden, there was a rather high utilization of physicians in all runs. In Germany and the Netherlands, neuropsychologists were more involved in Runs 2 and 3, while nurses did most of the work in Spain in Run 3. At memory clinics (WP3) (Supplementary Table 10), there was large variability in the time spent by different staff-types (lowest in Sweden, 180 minutes to more than 600 minutes in the Netherlands). In total, there were 400 MRI investigations at WP3 (Supplementary Table 11), and MRI was performed on almost all persons at WP3. In contrast, there were much fewer CSF analyses conducted because CSF was not mandatory in MOPEAD.

Costs and consequences

Run 4 had the lowest cost/TP (1,102 €), followed by Run 3, Run 2, and Run 1 (Table 2). The cost per screened and per positive screen was lowest in Run 1.

The cost per positive screen and evaluated at the full diagnostic at memory clinics (WP3) was lowest in Run 4, followed by Run 3. However, the differences between Runs 1 and 2 were very small for the cost per TP of positive screen. For costs per TP at WP3, the costs were higher in Run 2 than in Run 1.

There were great differences in the cost-consequence analysis between the countries (Supplementary Table 12). Since no TPs were identified in Germany in Run 1 or in Sweden and the Netherlands in Run 4, it was not possible to calculate the cost effectiveness. The cost effectiveness also highly depends on the number of TPs versus the number of screened, which explains some of the high costs per TP in some runs and countries.

Table 2
Cost effectiveness outcomes of the different Runs – all countries aggregated. Costs as Euros (€) 2019.

	Cumulative run cost	Cumulative WP3 cost	Cumulative total cost	Cost per screened	Cost per positive screen	Cost per evaluated at WP3	Cost per TP of AD	Cost per TP of screened positive	Cost per TP of evaluated at WP3
Run 1	89,872	62,742	152,613	103	279	1,677	3,115	2,042	1,480
Run 2	100,588	122,629	223,217	338	971	1,386	2,722	1,869	1,742
Run 3	16,545	72,200	88,746	204	465	944	1,530	1,319	1,255
Run 4	17,836	38,112	55,947	212	366	999	1,190	1,102	960

Table 3
Sensitivity analyses (S1-S3) of the cost effectiveness analysis

	Cumulative Run cost	Cumulative WP3 cost	Cumulative Total cost	Cost per screened	Cost per positive screen	Cost per evaluated at WP3	Cost per TP of AD
Base case							
Run 1	89,872	62,742	152,613	103	279	1,677	3,115
Run 2	100,588	122,629	223,217	338	971	1,386	2,722
Run 3	16,545	72,200	88,746	204	465	944	1,530
Run 4	17,836	38,112	55,947	212	366	999	1,190
S1							
Run 1	89,872	59,815	149,687	101	274	1,645	3,055
Run 2	63,114	119,688	182,802	277	795	1,135	2,229
Run 3	16,253	67,672	83,924	193	439	893	1,447
Run 4	16,634	36,644	53,278	202	348	951	1,134
S2							
Run 1	89,872	55,780	145,652	98	266	1,601	2,972
Run 2	52,856	110,916	163,772	248	712	1,017	1,997
Run 3	13,130	61,992	75,121	173	393	799	1,295
Run 4	9,809	33,813	43,622	165	285	779	928
S3							
Run 1	89,872	62,051	151,923	102	278	1,669	3,100
Run 2	97,884	125,412	223,297	338	971	1,387	2,723
Run 3	37,709	70,450	108,158	249	566	1,151	1,865
Run 4	29,985	37,881	67,866	257	444	1,212	1,444

In the GLM model (Supplementary Table 13), age, gender, and MMSE were not significant as background variables. Thus, the final model was applied only for the variables run and country. The model reflected the great heterogeneity between both runs and countries. The differences between the cost per TP and costs per screened case also reflects the large differences between countries and runs in identified TPs. The high odds ratio for the Netherlands is because few TPs were diagnosed at the full diagnostic at memory clinics (WP3).

Sensitivity analysis

The various approaches in the sensitivity analyses (Table 3) resulted in some changes, but the main results from the base case are rather stable: Runs 3 and 4 are more cost-effective than Runs 1 and 2. However, the differences between Runs 1 and 2 are small in sensitivity 3 and similar to the base case. Run 2 costs are much lower in sensitivity 1 and 2. Note that the only change for costs of Run 1 here is based on the change of costs at memory clinics (WP3).

The different options in Run 1 result in a range between €1,557–3,427 per TP of AD (Table 4). Even if the application is free (no cost), the cost per TP is higher than for Runs 3 and 4, but if the NNS is halved (TPs doubled), the cost per TP is similar for Runs 3 and 4.

The imputation of TPs in runs and countries where it was zero had minor effects on the outcome irrespective using a mean value or a value of 1 for imputation (Table 5). Total costs did not change. This imputation had only effects on the TP outcomes. By imputation, the cost/TP difference between Runs 1 and 2 got smaller.

In Supplementary Tables 14 and 15, the country specific results of the sensitivity analyses are presented.

The GLM model was also applied on S3 with small differences as compared to the base case (data not shown).

Table 4
Sensitivity analysis of Run 1 (S4)

S4 Run 1	Cumulative Run cost	Cumulative WP3 cost	Cumulative total cost	Cost per screened	Cost per positive screen	Cost per evaluated at WP3	Cost per TP of AD
Cost of application = 0	54,872	62,742	117,614	79	215	1,292	2,400
Full price of the application	105,181	62,742	167,923	113	307	1,845	3,427
Double TPs	89,872	62,742	152,613	103	279	1,677	1,557

Table 5
Sensitivity analysis S5: imputation instead of zero TPs

	Cost per TP of AD	Cost per TP of screened pos	Cost per TP at WP3
Base case			
Run 1	3,115	2,042	1,480
Run 2	2,722	1,869	1,742
Run 3	1,530	1,319	1,255
Run 4	1,190	1,102	960
Impute mean			
Run 1	2,807	1,836	1,328
Run 2	2,705	1,858	1,732
Run 3	1,525	1,310	1,247
Run 4	926	855	744
Impute value of 1			
Run 1	3,046	1,992	1,441
Run 2	2,705	1,858	1,732
Run 3	1,525	1,310	1,247
Run 4	1,138	1,051	914

DISCUSSION

Main findings

Using MOPEAD's explorative and innovative approach for testing the costs and consequences of identification of hidden MCI-due-to-AD and AD dementia persons, we found large variability across Europe and in the different pre-screening runs. Using this innovative method, we also detected multiple methodological challenges which is why we also conducted a comprehensive sensitivity analysis. Runs 3 and 4 had the lowest costs per TP/screened population, but the capacity of Runs 3 and 4 to identify cases with AD-risk must be discussed. Today there are great concerns regarding the capacity of the health systems in different countries to identify persons with dementia. The capacity is also even more questionable for MCI and other predementia conditions. If a disease modifying treatment would be available (such as FDA's conditional approval of aducanumab in June 2021), these challenges would of course be much greater [12, 13], which is also highlighted by the reports from RAND [14, 15]. Hence new diagnostic strategies (Runs 1 and 2) may be valuable after modifications.

Methodological considerations

Is early diagnosis of AD possible?

Our paper implicitly assumes that it is possible to set an early AD diagnosis, which reflects a common view in AD research [16, 17]. However, concerns and doubts whether this is possible have been raised [18–20]. It is important to bear in mind this discussion about diagnostic uncertainty, particularly if early AD diagnostics expand to a great scale. Issues such as predictive values, risk for false-positive and false-negative cases must be considered [12]. New blood-based biomarkers are useful tools [17], but it is important to know that such methods only can indicate a risk of AD, and that a suspected AD diagnosis must be confirmed or rejected with more comprehensive testing (for example at the memory clinics similar to WP3).

Due to logistical problems and because of various delays until ethical approval in some countries, the period for campaigning and recruitment varied between the countries. There were large differences between the countries in terms of recruitment success, attendance, pre-screening outcomes, and the numbers of identified AD persons, and thus the cost effectiveness of the different runs. If a large number of persons are screened but few persons are diagnosed with AD, the cost per identified case will be very high. Consequently, the cost effectiveness in terms of the cost per identified case with AD will be low in comparisons with a situation where the number of identified cases is high (given the assumption that the screening costs are rather similar). Due to the design of MOPEAD, it was presumed that approximately 100 persons were needed to be screened in order to reach the 33 positive cases that were planned per run and site to be evaluated at the memory clinics (WP3). However, even if more than 33 screened positive, these persons beyond these 33 could not be referred to WP3 because of the design and budget limitations of MOPEAD.

There were also variabilities in the types of staff and the time use between the runs and countries. This might reflect the different ways we work in different parts of Europe, but it might also reflect differences in the implementation of the runs in different countries, such as the use of neuropsychologists. For example, in Germany and the Netherlands, neuropsychologists or nurses were present at the doctors' offices in Runs 3 and 4 to carry out the pre-screening procedures. Thus, the sensitivity analysis used different approaches to adjust for these probable project-driven implementation differences.

Specific Run comments

In Run 1 (the web-approach), the ability to identify TP of AD dementia or MCI due to AD of such applications is also crucial, and further studies on the cognitive tests in such applications, cut-offs, etc., are needed. Run 1 had the lowest proportion of TPs, which was expected when a general population of elderly with an interest in knowing their cognitive status is offered cognitive testing. However, the detection rate needs to be improved. The pricing per user is yet unclear. Run 1 (similar to Run 2) also needed some campaigning activities (with accompanying costs) for the recruitment. There are already several similar applications available on "the web market" and more will probably enter. Although very hypothetical and simplified, if the NNS/TP in Run 1 could be halved, the cost per TP and screened would be on the same magnitude as in Runs 3 and 4, indicating the potential of Run 1.

The cost per identified case in Run 1 was high, mainly because of the low detection rate. On the other hand, the lowest cost per screened case was in Run 1. One specific problem in Run 1 was the low attendance rate of those that screened positive (21% as compared to 37–74% in the other Runs). Run 1 has no face-to-face strategy. The main reasons for low attendance are due to the logistical problems in contacting those who screened positive in Run 1 (due to lack of contact information in line with data protection regulations) and encouraging them to enter a memory clinic. The proportion of these persons who screened positive and were lost to follow-up that would end up as TPs is of course unknown. It is also unknown how people who screened positive but were lost to follow-up experienced this situation. There are also people that did not complete Run 1 for many reasons. This was a phenomenon that occurred in all countries. Drop out reasons for Run 1 are seen in Supplementary Table 16.

Run 2 (Open-House) was rather efficient in terms of memory clinic attendance (WP3) and TP identification, but also rather expensive. The high costs were driven by involvement of many staff-types (physicians, nurses, neuropsychologists) in the pre-screening stage. If primarily specially trained nurses were deployed, the costs could be lowered.

Since Run 2 events predominantly took place at specialist clinics, it should be feasible to integrate the work. A direct link between the Open House and the specialist clinic would lower the costs.

Run 3 (primary care) had similar levels of TP as Runs 2 and 4 and rather low costs per TP (a bit higher than Run 4). Run 3 is today the most common entrance to the diagnostic work up when someone (patients, family) has raised the question about dementia. If disease modifying treatments (DMT) enter the market, the number of patients that would seek primary care for a suspected AD-dementia or MCI due to AD would probably increase. Key issues are the working conditions and reimbursement systems in primary care [21], which vary across Europe. A system where pay-per-visit dominates, disincentives work with people with a suspected AD. Thus, it is an important policy-making issue to change the reimbursement system in primary care to make work with AD (and other time-demanding long-term chronic conditions) properly valued. Another important issue is to improve competence (diagnosis, management) in cognitive disorders in primary care.

Run 4 (diabetes specialists) had the greatest proportion of cases with AD (18%), which supports the notion that Type 2 diabetes is a risk factor for dementia, and it also indicates that clinics with Type 2 diabetes (endocrinology, internal medicine, primary care, etc.) might be an important source for the early detection of AD. However, although Run 4 offers an interesting way to identify people with cognitive disorders, its capacity to play an important role in terms of volumes of patients is probably limited. Run 4 experienced the greatest problems in recruiting patients to MOPEAD, particularly in Sweden, the Netherlands, and Germany. In two countries, Sweden and the Netherlands, no persons with AD were identified at memory clinics (WP3) from this run. This was due to a different population in the diabetes clinic, with the regular diabetes patients being managed by the general practitioner and primarily younger complex patients visiting the specialist hospitals. The large country differences in Run 4 also reflect the heterogeneity in how Type 2 diabetes is managed in the five countries.

Cut-offs

Besides the logistical challenges, the most effective cut-off for screened positive needs to be determined. There was a gradient in the proportion of positive screens with the algorithm, 35–58%, with the lowest in Run 2 and the highest in Run 4. This is as expected because of the profile of those who participated in the different runs. However, the proportion of TPs of those screened was low, average 8%, and 21% of positive screens, indicating that the cut-offs in the algorithm did not work optimally. However, this experience also illustrates the explorative nature of MOPEAD in identifying early cases of AD. The risk of being an early unidentified case of early AD is probably higher in the MOPEAD Runs than in a general population, but the way to identify these persons was one of the challenges in MOPEAD. For example, if a person experienced a subjective memory problem, was worried about this and had a high Cardiovascular Risk Factors, Aging, and Incidence of Dementia risk score [9, 22], but scored 30 on the cognitive screening test MMSE, this resulted in a positive screen. The Cardiovascular Risk Factors, Aging, and Incidence of Dementia risk score [9, 22] indicates a risk for future dementia, but not necessarily for the current moment. Therefore, while the cut-offs for this pre-screening strategy might be useful to identify at-risk subjects, the probability to detect a TP in the diagnostic evaluation is presumably decreased. In any screening program, there are trade-offs in the setting of cut-offs for a positive screen. Too "generous" to avoid false negatives will put a burden for follow-ups, too "restrictive" will result in more false negative (missed TPs) cases. In MOPEAD, the screening cut-offs may have been set too low, resulting in a high proportion of false positive cases. There is no easy solution in this area. MOPEAD is a pioneering explorative project in that sense and has provided data to inform these discussions.

Attitudes

Another observation is that the proportion of those who screened positive and attended WP3 was rather low, 36% on average. There is support in publications that people wish to know whether they have dementia or not [23, 24]. Our data do not entirely support this view (even after taken the logistic problems into consideration). There may be many reasons for that. In Runs 3 and 4, consecutive patients were offered participation in MOPEAD. The visit for most of these patients was not because of memory problems or fear for AD/dementia, and these persons were thus probably less interested in further diagnostic work ups. Consecutive patients who visited the clinics in Runs 3 and 4 and potentially were eligible had more comorbidities and they were also more often less healthy than those in Runs 1 and 2. Their interest was more focused on the reason why they visited the clinic rather than early AD diagnostics. In Run 1 (with the lowest participation at WP3, 21%), it is hard to know why people participated or not. Given that it was easy to take an online cognitive test, it is possible that many participated out of curiosity with less commitment to the underlying project. In addition, trust in online applications might be lower, especially in older people. In Run 2, however, the attendance at WP3 was rather high, 70%, probably because of the direct link between the Open-House initiative and WP3 for further diagnostics. Another reason for the high attendance rate from Run 2 is probably that those who visited the Open House had concerns about their memory. However, it is necessary to keep in mind that if a person gets a confirmed diagnosis of AD/dementia, it may have negative consequences in terms of insurance, driving, weapon and profession licenses, stigmatization, etc. This may also influence the willingness to undergo a further diagnostic work up at WP3.

Another reason for the rather low attendance at WP3 might be the fact that we so far have no DMT for AD on the market. If that would be the case, with hope for efficient treatment, the attendance rate at WP might be higher.

Resources

Another critical issue is the capacity of specialist clinics. Although the focus in MOPEAD is on the runs, it is obvious that there will be an increase in the need of specialist diagnostic work ups if a DMT enters the market. Even today, with the traditional way of referrals (as from Runs 3 and 4) there are waiting lists and the capacity in imaging and CSF analyses is limited. It must be discussed how to handle people that screen positive particularly in Run 1, but also Run 2. The numbers of people with a suspected AD that might come from pathways like Run 1 and 2 are unknown, so the discussions about cut-offs and logistics is not just a technical discussion.

"Real world"

Based on the explorative approach in MOPEAD and the results of the cost-consequence analysis, combined with the methodological and logistic issues, it is not easy to state which run would fit best in the

"real world", particularly in a situation where a DMT would be present [12].

Due to the design of MOPEAD, it was somewhat difficult to differ between resource use and costs that would reflect a "real world" application of the Runs and project-driven results. In the sensitivity analyses we tried to better reflect the "real world". We regard Sensitivity 3 as "the best guess" and the option that best reflects a "real world" situation, since here more side costs and overhead costs for Runs 2–4 are included. Even with this option, the results are similar to the base case. However, more implementation studies are needed to make the process of early detection more effective.

CONCLUSIONS

The results of MOPEAD are implicitly linked to the expectations and hopes for a DMT of AD. Without an effective DMT, it is hardly recommended to focus on screening programs for early detection of AD, and there are also no such recommendations within EU so far. To avoid false positive cases, it is also important to continue improving diagnostic accuracy.

The care structure and the capacity of the different runs in different countries need to be considered. Runs 3 and 4 would not have enough capacity to handle a situation with a great demand for early AD/dementia diagnostics. Furthermore, Run 4 also only covers a small, although important, segment of the population at risk for AD-dementia or AD due to MCI. Thus, a combination strategy seems to be appropriate, which needs adaptation to the country-specific circumstances.

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SUPPLEMENTARY MATERIAL

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