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FEATURED ARTICLE

Complementary pre-screening strategies to uncover hidden prodromal and mild Alzheimer's disease: Results from the MOPEAD project

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Abstract

Introduction: The Models of Patient Engagement for Alzheimer's Disease (MOPEAD) project was conceived to explore innovative complementary strategies to uncover hidden prodromal and mild Alzheimer's disease (AD) dementia cases and to raise awareness both in the general public and among health professionals about the importance of early diagnosis.

Methods: Four different strategies or RUNs were used: (a) a web-based (WB) pre-screening tool, (2) an open house initiative (OHI), (3) a primary care–based protocol for early detection of cognitive decline (PC), and (4) a tertiary care–based pre-screening at diabetologist clinics (DC).

Results: A total of 1129 patients at high risk of having prodromal AD or dementia were identified of 2847 pre-screened individuals (39.7%). The corresponding proportion for the different initiatives were 36.8% (WB), 35.6% (OHI), 44.4% (PC), and 58.3% (DC).

Conclusion: These four complementary pre-screening strategies were useful for identifying individuals at high risk of having prodromal or mild AD.

KEYWORDS
Alzheimer's disease, diagnostic gap, early diagnosis, patient engagement, population-based screening

1 | BACKGROUND

Alzheimer's disease (AD) is a devastating condition that not only greatly affects patient's health, but also poses an important burden on the patient's immediate family circle. For different reasons, many patients and clinicians fail to acknowledge the importance of an early clinical evaluation and diagnosis of this condition. Stigma around dementia and fear of the potential side effects from treatments or diagnostic tests make patients and caregivers avoid or delay seeking medical help. But even when they do, they may find that health care professionals do not prioritize reaching an early diagnosis given the perceived lack of efficacy of the limited number of pharmacological treatments available. Health care services may also be hindered by insufficient appointment time, inadequate training, and lack of knowledge about potential social care interventions. Consequently, there is a large proportion of individuals with cognitive decline that remain "hidden" or undiagnosed in their communities. Without a proper clinical evaluation of their cognitive problem, these patients might remain undiagnosed until very advanced stages of the disease.

Recent data confirm that the first pathological changes of AD begin many years before the onset of the clinical symptoms. It has been hypothesized that early initiation of treatment should increase the chances of modifying the disease progression.[1] Along these lines, there is some evidence suggesting that minimizing the time from first symptoms to first visit improves the survival in patients with dementia.[2] Nevertheless, as long as patients remain undiagnosed, they have no access to pharmacological treatments of any kind, including experimental treatment from clinical trials, or to support

services. In addition, they are less likely to have the opportunity to make relevant decisions in the disease stages when their cognitive capacity still allows. This includes health, financial, and social decisions aimed at minimizing the strain of this condition on the patients and their caregivers. Thus early detection of AD in the prodromal or mild dementia stages has benefits at many different levels[3] that are currently denied to a large proportion of patients. In this context, the Models of Patient Engagement for Alzheimer's Disease (MOPEAD) project was conceived to explore innovative complementary strategies to uncover these hidden cases and to raise awareness both in the general public and among health professionals about the importance of early diagnosis of cognitive impairment.[4] Here we describe and discuss the results of these prescreening initiatives.

2 | METHODS

Memory clinics located in Ljubljana (Slovenia), Barcelona (Spain), Stockholm (Sweden), Amsterdam (The Netherlands), and Cologne (Germany) participated in the project. Four innovative pre-screening strategies (or RUNs) were implemented to detect cognitive decline among eligible individuals: (1) a web-based pre-screening tool, (2) an open house initiative (OHI), (3) a primary care–based protocol for early detection of cognitive decline, and (4) a tertiary care–based pre-screening at diabetologist clinics. Pre-screening took place between May 2018 and May 2019. Although typically participants had some degree of concern about their cognitive abilities, only individuals ages 65 to 85 years who had never received a dementia-related diagnosis

were eligible to participate. A positive pre-screening result indicated that individuals were at high risk of having prodromal AD or mild AD dementia. Referral for a full clinical evaluation at the memory clinics was offered to these individuals. Those patients with evidence of advanced dementia (eg, Mini-Mental State Exam [MMSE] score below 20) were also classified as having a positive pre-screening result in all initiatives but were referred to the usual channels of the health system in place, since MOPEAD focused on prodromal and mild AD dementia.

The web-based pre-screening tool (WB) has been described in detail elsewhere.[5] Briefly, this citizen science initiative consisted of an online marketing campaign aimed at redirecting eligible individuals to a web platform. There, individuals received information about AD and were asked to participate in the project. Two tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd) were selected to identify patients at high risk for prodromal AD and dementia among those who agreed to participate. A positive pre-screening result was defined as a scoring below the prefixed cutoff on the online cognitive tests, adjusted by age and education.

OHIs seek to make specialized memory clinics accessible to anyone worried about their memory, avoiding the usual requirement for a doctor referral. OHIs were implemented in all participating memory clinics, offering eligible individuals a free cognitive screening that included a MMSE,[6,7] the picture version of the Free and Cued Selective Reminding Test,[8] and specific qualitative questions to assess subjective cognitive decline (SCD).[9,10] One of the participating memory clinics (Fundació ACE) has been successfully implementing this initiative since 2008, resulting in the diagnosis of at least 87 AD dementia cases, 736 individuals with mild cognitive impairment (MCI), and 1660 with SCD from its inception.[11] Individuals with an MMSE score between 20 and 27, significant memory impairment according to the Free and Cued Selective Reminding Test total score, or subtle memory impairment in this test along with three positive answers to the SCD questions were considered to have a positive pre-screening result.

The primary care–based patient engagement initiative (PC) consisted of implementing a protocol for early detection of cognitive decline using easily administered tools at collaborating primary care practices. The idea was to take advantage of the great patient accessibility of the primary care practices to perform this onsite pre-screening during a regular visit. The tools that were administered in this initiative included the MMSE, a new version of the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE), and the same set of SCD specific questions used in the OHI. Individuals meeting one of the following criteria were considered to have a positive pre-screening result in this PC initiative: MMSE score between 20 and 27, a new CAIDE risk score suggesting high risk of dementia, or a new CAIDE risk score suggesting medium risk of dementia along with three positive answers to the SCD questions.

Finally, the diabetologists clinic–based patient engagement initiative (DC) relied on the known increased risk of cognitive impairment and dementia, both vascular and AD, among patients with diabetes mellitus.[12,13] It comprises implementation of a protocol designed specifically to assess the risk of prodromal AD and dementia among patients attending diabetologist clinics. This protocol included the

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed existing literature describing the importance of early diagnosis of Alzheimer's disease (AD) using PubMed. These relevant citations are appropriately cited.

2. **Interpretation**: The results of the four novel pre-screening initiatives implemented within the Models of Patient Engagement for Alzheimer's Disease (MOPEAD) project confirm the ability of these tools to reveal hidden cases of prodromal or mild AD dementia. Furthermore, the profile of individuals undergoing these pre-screenings differed between initiatives, underscoring the complementarity of these approaches.

3. **Future directions**: These results indicate that the use of several complementary pre-screening strategies should be considered when promoting early diagnosis of AD. Population-based initiatives such as web-based pre-screenings that do not depend on traditional referral circuits (ie, primary or specialized care) should be favored to capture younger and healthier patients (with a lower background risk of dementia). Validation studies of these pre-screening initiatives are already underway.

MMSE, the three-question SCD assessment, the diabetes-specific dementia risk score (DSDRS),[14] and data on diabetes-related complications and hypoglycemia via a questionnaire developed specifically for MOPEAD. Individuals with MMSE score between 20 and 27, a DSDRS score indicating high risk of dementia, or a DSDRS indicating medium risk of dementia along with three positive answers to the SCD questions were considered to have a positive pre-screening.

2.1 | Statistical analyses

Individuals who completed the different pre-screening initiatives and those with a positive pre-screening result were described in terms of age, sex, and study site (country). We also described patients in terms of the results of the MMSE and SCD assessments when this information was available (OHI, PC, and DC initiatives only). We assessed how age, sex, MMSE scores, and frequency of SCD varied between participants of each initiative and between study sites by using multivariable regression models: analysis of variance (ANOVA; age and MMSE) and unconditional logistic regression (sex and SCD). We also explored the likelihood of receiving a positive pre-screening result as a function of the prescreening initiative, age, sex, and the study site by using unconditional logistic regression models. F-tests were used to assess statistical significance in ANOVA test, whereas Likelihood Ratio (LR) and Wald tests were used to assess statistical significance in unconditional logistic regression models.

TABLE 1 Mean age among individuals who completed the different initiatives (RUNs) by country and sex

		RUN 1 (WB)		RUN 2 (OHI)		RUN 3 (PC)		RUN 4 (DC)		ALL RUNS	
		N	Mean age (SD)	N	Mean age (SD)	N	Mean age (SD)	N	Mean age (SD)	N	Mean age (SD)
All	Slovenia	653	69.2 (4.7)	83	71.7 (4.7)	65	72.3 (5.2)	91	73.1 (5.3)	892	70.1 (5.0)
	Spain	528	70.5 (5.4)	101	73.7 (5.1)	105	73.9 (5.3)	109	73.0 (5.4)	843	71.6 (5.5)
	Sweden	125	71.7 (5.1)	118	73.7 (5.4)	99	75.3 (5.4)	39	74.5 (5.5)	381	73.5 (5.5)
	Netherlands	140	71.7 (5.7)	181	72.0 (5.0)	77	73.2 (5.3)	12	72.8 (5.5)	410	72.1 (5.3)
	Germany	41	68.0 (4.4)	178	72.8 (5.7)	89	74.4 (5.9)	13	72.9 (3.8)	321	72.6 (5.9)
	Total	1487	70.1 (5.2)	661	72.7 (5.3)	435	74.0 (5.5)	264	73.3 (5.3)	2847	71.6 (5.5)
Female	Slovenia	449	69.0 (4.6)	48	71.1 (4.2)	38	72.5 (5.4)	44	73.1 (5.5)	579	69.7 (4.9)
	Spain	234	69.7 (5.2)	70	73.7 (5.1)	62	73.5 (5.0)	51	73.3 (5.7)	417	71.4 (5.5)
	Sweden	77	71.7 (4.8)	77	73.9 (5.7)	59	75.2 (5.8)	10	74.4 (4.9)	223	73.5 (5.5)
	Netherlands	96	71.5 (5.8)	125	71.3 (4.7)	33	73.4 (5.7)	4	73.0 (4.5)	258	71.6 (5.3)
	Germany	26	67.5 (3.3)	108	72.7 (6.1)	57	74.6 (6.0)	7	73.7 (3.9)	198	72.6 (6.1)
	Total	882	69.6 (5.0)	428	72.5 (5.4)	249	74.0 (5.6)	116	73.3 (5.4)	1675	71.3 (5.5)
Male	Slovenia	204	69.8 (5.0)	25	72.4 (5.0)	27	72.1 (4.9)	47	73.1 (5.2)	303	70.7 (5.2)
	Spain	294	71.1 (5.4)	31	73.5 (5.1)	43	74.4 (5.8)	58	72.8 (5.2)	426	71.8 (5.5)
	Sweden	48	71.6 (5.7)	41	73.3 (4.9)	40	75.6 (4.8)	29	74.5 (5.8)	158	73.6 (5.5)
	Netherlands	44	72.3 (5.5)	49	73.3 (5.3)	40	73.1 (5.1)	8	72.6 (6.2)	141	72.9 (5.3)
	Germany	15	68.9 (5.8)	67	72.9 (5.3)	30	74.0 (5.7)	6	72.0 (3.9)	118	72.6 (5.5)
	Total	605	70.7 (5.4)	213	73.1 (5.1)	180	74.0 (5.4)	148	73.2 (5.3)	1146	72.0 (5.5)

Analysis of variance (ANOVA) model including: RUN (F = 59.4; $P < .001$), sex (F = 4.3; $P = .013$), and country (F = 12.8; $P < .001$).

3 | RESULTS

A total of 2847 individuals were prescreened in one of these initiatives. More than half of these patients completed the WB prescreening (n = 1487; 52%) whereas OHI, PC, and DC initiatives prescreened 661, 435, and 264 subjects, respectively. The number of individuals prescreened per country ranged from 892 in Slovenia to 321 in Germany (see Table 1). We observed age differences between countries and scenarios (RUNs), both among pre-screened patients and among the subset with a positive result. Thus individuals pre-screened in the WB initiative were the youngest (mean = 70.1 years, SD = 5.2), followed by those pre-screened in the OHI (mean = 72.7 years, SD = 5.3). In contrast, those pre-screened in the PC and DC initiatives were older, with mean ages of 74.0 years (SD = 5.5) and 73.3 years (SD = 5.3), respectively. These differences were statistically significant even after adjusting by sex or country of origin (F = 59.4, $P < .001$). The proportion of individuals ages 80 and older was 10.9% and varied across the different initiatives (6.6% in WB, 13.6% in OHI, 19.5% in PC, and 14.0% in DC). We found that mean age was lowest among individuals pre-screened in Slovenia (mean = 70.1 years, SD = 5.0) and highest among those from Sweden (mean = 73.5 years, SD = 5.5). Although this result could be partially explained by the proportion of individuals undergoing WB pre-screening (73% in Slovenia compared to 32% in Sweden) we found that after adjustment by pre-screening strategy and sex, these differences remained (F = 12.8, $P < .001$). In fact, participants from Sweden had the oldest mean age in all initiatives (Table 1). Remark-

ably similar trends in mean age across initiatives and countries were observed in the subset of patients with a positive pre-screening result (Table 2).

Overall, more women than men completed these pre-screening RUNs (59.4%). However, as shown in Table S1, this result varied greatly depending on the initiative (LR = 33.2, $P < .001$) and country (LR = 45.5, $P < .001$). Thus although 66.8% of participants in the OHIs were female, the proportion of females among those pre-screened in the DC initiative was only 43.9%. Between countries, Spain presented the lowest proportion of female participants overall (49.5%), a result driven partially by the low observed proportion of female participants pre-screened in the WB initiative (44.3% in Spain, when in all other countries this proportion exceeded 60%), and Slovenia presented the highest proportion of female participants (65.6%). These same trends for countries and strategies were observed among patients with a positive pre-screening result (Table 3), although the overall proportion of female participants was slightly lower in this subset (56.6%).

Among the three pre-screening initiatives that included MMSE and SCD assessments (OHI, PC, and DC; Tables 4 and 5), we found the highest MMSE score estimates among those individuals from the OHI (mean = 28.1, SD = 2.1) and the lowest MMSE score estimates among those pre-screened in the DC initiative (mean = 27.1, SD = 2.5). These differences were statistically significant after adjusting for age, sex, and country (F = 6.4, $P = .002$). As for the proportion of patients who answered positively all three SCD questions, we found that SCD was most frequent among those individuals pre-screened in

TABLE 2 Mean age among individuals with a positive pre-screening in the different initiatives (RUNs) by country and sex

		RUN 1 (WB)		RUN 2 (OHI)		RUN 3 (PC)		RUN 4 (DC)		ALL RUNS	
		N	Mean age (SD)	N	Mean age (SD)	N	Mean age (SD)	N	Mean age (SD)	N	Mean age (SD)
All	Slovenia	225	69.1 (4.6)	47	71.9 (5.1)	38	73.5 (5.0)	49	73.4 (5.8)	359	70.5 (5.2)
	Spain	191	71.1 (5.5)	54	75.2 (4.9)	57	74.3 (5.0)	75	74.7 (5.4)	377	72.9 (5.6)
	Sweden	43	72.6 (5.2)	30	73.5 (6.0)	36	76.1 (5.0)	18	76.3 (5.4)	127	74.3 (5.5)
	Netherlands	74	72.4 (5.8)	56	73.3 (4.9)	40	74.3 (4.8)	6	73.2 (4.7)	176	73.2 (5.3)
	Germany	14	71.6 (5.5)	48	73.2 (6.2)	22	74.6 (5.6)	6	74.3 (3.3)	90	73.4 (5.8)
	Total	547	70.6 (5.3)	235	73.5 (5.4)	193	74.5 (5.0)	154	74.4 (5.4)	1129	72.4 (5.6)
Female	Slovenia	157	68.7 (4.4)	23	71.3 (4.8)	21	73.6 (4.9)	24	73.1 (6.4)	225	69.9 (5.1)
	Spain	75	70.0 (5.6)	35	75.1 (5.0)	38	73.9 (4.8)	36	75.2 (5.6)	184	72.8 (5.8)
	Sweden	22	72.4 (5.4)	19	72.8 (6.4)	20	76.3 (4.6)	6	75.3 (5.7)	67	73.9 (5.7)
	Netherlands	49	72.4 (5.8)	40	73.0 (5.0)	16	74.1 (5.0)	3	71.0 (2.6)	108	72.8 (5.3)
	Germany	7	70.7 (4.0)	30	73.8 (6.6)	10	74.7 (6.7)	3	73.3 (4.9)	50	73.5 (6.2)
	Total	310	69.9 (5.2)	147	73.4 (5.6)	105	74.4 (5.0)	72	74.3 (5.8)	634	72.0 (5.7)
Male	Slovenia	68	70.1 (4.8)	19	72.4 (4.9)	17	73.5 (5.3)	25	73.8 (5.2)	129	71.6 (5.1)
	Spain	116	71.8 (5.3)	19	75.5 (4.9)	19	74.9 (5.4)	39	74.3 (5.2)	193	73.0 (5.4)
	Sweden	21	72.9 (5.1)	11	74.6 (5.2)	16	75.8 (5.6)	12	76.8 (5.4)	60	74.8 (5.4)
	Netherlands	25	72.6 (5.9)	16	74.1 (4.6)	21	74.6 (5.0)	3	75.3 (5.8)	65	73.7 (5.2)
	Germany	7	72.4 (7.0)	18	72.1 (5.4)	11	73.8 (4.3)	3	75.3 (0.6)	39	72.9 (5.2)
	Total	237	71.5 (5.3)	83	73.7 (5.1)	84	74.6 (5.1)	82	74.6 (5.1)	486	72.9 (5.4)

Analysis of variance (ANOVA) model for age including: RUN (F = 32.5; P < .001), sex (F = 2.7; P = .069), and country (F = 9.7; P < .001).

the OHI (39.2%), followed by those pre-screened in the DC initiative (36.4%) and less frequent among those pre-screened in the PC initiative (20.0%). These differences remained statistically significant after adjusting for age, sex, and country (LR = 74.0, P < .001). Notably, the proportion of SCD varied greatly between countries irrespective of the pre-screening initiative (LR = 157.7, P < .001), being lowest for The Netherlands (13.3%) and highest for Spain (55.6%).

Overall, we found that 39.7% (n = 1129) of all pre-screened individuals had a positive result. Among them, we identified a total of 16 individuals with evidence of advanced dementia in the OHI (n = 7), PC (n = 5), and DC initiatives (n = 4). The proportion of individuals with a positive result was higher among patients undergoing DC and PC pre-screening (58.3% and 44.4%, respectively) and lower among participants of the OHI (35.6%) and WB initiatives (36.8%) (see Table S2). We found that these differences were statistically significant after adjusting for age, sex, and country. Thus patients undergoing a PC pre-screening were 46% more likely to have a positive result than those participants of the WB strategy, whereas the likelihood of having a positive result among those prescreened in diabetologist clinics was more than twice that of those pre-screened in the WB initiative (Table 6). We also found that the probability of a positive prescreening result was not the same across countries. Thus after adjusting for age, sex, and initiative, those participants from Slovenia, Spain, and The Netherlands were more likely to have a positive prescreening result (40.2%, 44.7%, and 42.9%) than those from Germany (28.0%). Finally, the likelihood of a positive pre-screening

result seems to increase with age but was not influenced by sex (Table 6).

4 | DISCUSSION

The four patient engagement initiatives within the MOPEAD project were able to detect a total of 1129 individuals at high risk of having prodromal AD and dementia. Patients with a positive pre-screening result qualify for a full clinical evaluation that will ultimately determine their clinical diagnosis. Therefore, thanks to these pre-screening initiatives, these patients will have the opportunity to receive an earlier diagnosis with all the benefits this entails.

We have shown how the profile of patients with a positive pre-screening result differs between the four initiatives analyzed. Although this might partially be due to the slightly different tests being used and the positivity criteria followed by each initiative, there is no question that each initiative targeted different populations. In fact, we observed age and sex differences between initiatives among individuals who completed the pre-screening, irrespective of whether their result was positive or not. Thus although only individuals aged between 65 and 85 years of age (a relatively narrow age range) were eligible to participate in these initiatives, we found that patients completing the WB pre-screening tended to be younger, whereas patients completing the DC initiative tended to be older and also mostly male. Of interest, the proportion of pre-screened individuals ages 80 to 85 was lower in the DC

TABLE 3 Proportion of female sex among individuals with a positive pre-screening in the different RUNs by country

Age	Country	RUN 1 (WB)	RUN 2 (OHI)	RUN 3 (PC)	RUN 4 (DC)	ALL RUNS
All	Slovenia	69.8%	54.8%	55.3%	49.0%	63.6%
	Spain	39.3%	64.8%	66.7%	48.0%	48.8%
	Sweden	51.2%	63.3%	55.6%	33.3%	52.8%
	Netherlands	66.2%	71.4%	43.2%	50.0%	62.4%
	Germany	50.0%	62.5%	47.6%	50.0%	56.2%
	Total	56.7%	63.9%	55.6%	46.8%	56.6%
65-69 years	Slovenia	73.0%	63.2%	50.0%	60.0%	69.9%
	Spain	48.9%	66.7%	63.6%	46.7%	51.2%
	Sweden	53.8%	80.0%	33.3%	33.3%	58.6%
	Netherlands	66.7%	76.9%	40.0%	100.0%	67.4%
	Germany	40.0%	62.5%	100.0%	NA	60.9%
	Total	63.1%	68.7%	55.2%	52.9%	62.6%
70-74 years	Slovenia	66.0%	40.0%	60.0%	40.0%	57.5%
	Spain	34.5%	69.2%	73.9%	43.5%	47.9%
	Sweden	50.0%	60.0%	58.3%	50.0%	54.5%
	Netherlands	70.0%	75.0%	45.0%	50.0%	62.5%
	Germany	75.0%	54.5%	33.3%	100.0%	51.7%
	Total	52.5%	62.7%	56.1%	45.8%	54.2%
75-79 years	Slovenia	61.8%	55.6%	60.0%	40.0%	57.1%
	Spain	19.2%	57.9%	60.0%	47.6%	42.1%
	Sweden	46.2%	50.0%	50.0%	33.3%	46.2%
	Netherlands	62.5%	58.8%	33.3%	NA	58.3%
	Germany	66.7%	45.5%	50.0%	25.0%	45.0%
	Total	47.8%	54.5%	54.3%	41.5%	49.6%
80-85 years	Slovenia	66.7%	50.0%	40.0%	55.6%	52.4%
	Spain	36.8%	69.2%	61.5%	56.3%	54.1%
	Sweden	60.0%	60.0%	63.6%	20.0%	53.8%
	Netherlands	63.6%	83.3%	44.4%	0.0%	59.3%
	Germany	0.0%	90.0%	60.0%	NA	70.6%
	Total	47.5%	73.7%	55.8%	48.4%	56.6%

Abbreviation: NA, Not available.
Logistic regression model for positive pre-screening including: RUN (LR[3df] = 34.0; $P < .001$), country (LR[4df] = 45.3; $P < 0.001$), age (LR[3df] = 39.9; $P < 0.001$), and sex (LR[1df] = 2.3; $P = .325$).

initiative than in the PC. Although higher mortality associated with diabetes could explain this finding, other reasons such as lower frequency of visits to a diabetes specialist (but not necessarily to primary care) of individuals ages 80 and above could also contribute.

An identical pattern was observed among those individuals with a positive pre-screening result. A previous study comparing SCD cases ascertained within an OHI with those identified after a doctor referral to a memory clinic showed that the former were younger, more likely to be female, more highly educated, with more frequent family history of dementia, and presented with higher MMSE scores.[15] The authors suggested that these marked differences could explain observed heterogeneity in the rates of progression to AD across studies and advised that the recruitment method of the partici-

pants should be considered when comparing the results of different studies.

Although this heterogeneity might represent a problem when combining evidence from different studies, it becomes an advantage when the goal is to promote earlier diagnosis of prodromal AD and mild AD dementia across all populations.

The ability of each strategy to capture specific target populations makes them quite complementary. Thus, although the population-based initiatives such as WB pre-screening and OHI can engage younger and healthier patients (with a lower background risk of dementia), patient-based initiatives (ie, PC and DC strategies) provide an excellent opportunity to engage patients with relevant co-morbidity who experience a higher risk of dementia.

TABLE 4 Mean MMSE among individuals who completed RUNs 2 through 4 by country and sex

| | | RUN 2 (OHI) | RUN 3 (PC) | RUN 4 (DC) | ALL RUNS (2-4) |
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
All	Slovenia	28.0 (1.6)	27.3 (2.7)	27.0 (2.4)	27.4 (2.3)
	Spain	26.4 (3.2)	27.4 (2.4)	27.4 (1.9)	27.1 (2.6)
	Sweden	28.8 (1.4)	27.6 (2.8)	27.1 (2.8)	28.1 (2.3)
	Netherlands	28.2 (2.0)	28.0 (1.7)	25.2 (5.7)	28.0 (2.3)
	Germany	28.8 (1.5)	28.5 (1.3)	26.7 (2.4)	28.6 (1.5)
	Total	28.1 (2.1)	27.8 (2.3)	27.1 (2.5)	27.8 (2.3)
Female	Slovenia	28.1 (1.6)	27.5 (2.9)	26.8 (2.6)	27.5 (2.4)
	Spain	26.2 (3.6)	27.1 (2.5)	26.9 (2.1)	26.7 (2.9)
	Sweden	28.7 (1.4)	27.9 (2.4)	26.6 (2.5)	28.3 (2.0)
	Netherlands	28.1 (1.9)	28.0 (2.1)	26.3 (1.9)	28.1 (1.9)
	Germany	28.8 (1.4)	28.6 (1.1)	27.1 (1.5)	28.7 (1.4)
	Total	28.1 (2.2)	27.8 (2.3)	26.8 (2.3)	27.8 (2.3)
Male	Slovenia	27.7 (1.7)	27.1 (2.5)	27.1 (2.2)	27.3 (2.2)
	Spain	26.7 (2.3)	27.9 (2.0)	27.8 (1.7)	27.6 (2.0)
	Sweden	28.8 (1.3)	27.2 (3.4)	27.3 (2.9)	27.8 (2.7)
	Netherlands	28.2 (2.5)	28.0 (1.4)	24.6 (7.0)	27.8 (2.9)
	Germany	28.7 (1.6)	28.3 (1.6)	26.2 (3.3)	28.4 (1.8)
	Total	28.2 (2.0)	27.7 (2.3)	27.3 (2.7)	27.8 (2.4)

Analysis of variance (ANOVA) model including: RUN (F = 6.4; P = .002), age (F = 84.4; P < .001), sex (F = 0.6; P = .542), and country (F = 14.7; P < .001).

TABLE 5 Individuals with positive answers to all three SCD questions among those who completed RUNs 2 through 4 by country and sex

| | | RUN 2 (OHI) | RUN 3 (PC) | RUN 4 (DC) | ALL RUNS (2-4) |
		SCD (%)	SCD (%)	SCD (%)	SCD (%)
All	Slovenia	49 (59.0%)	15 (23.1%)	9 (9.9%)	73 (30.5%)
	Spain	67 (66.3%)	30 (28.6%)	78 (71.6%)	175 (55.6%)
	Sweden	45 (38.1%)	24 (24.2%)	4 (10.3%)	73 (28.5%)
	Netherlands	31 (17.1%)	4 (5.2%)	1 (8.3%)	36 (13.3%)
	Germany	67 (37.6%)	14 (15.7%)	4 (30.8%)	85 (30.4%)
	Total	259 (39.2%)	87 (20.0%)	96 (36.4%)	442 (32.5%)
Female	Slovenia	31 (64.6%)	12 (31.6%)	7 (15.9%)	50 (38.5%)
	Spain	47 (67.1%)	18 (29.0%)	41 (80.4%)	106 (57.9%)
	Sweden	32 (41.6%)	16 (27.1%)	2 (20.0%)	50 (34.2%)
	Netherlands	23 (18.4%)	2 (6.1%)	0 (0.0%)	25 (15.4%)
	Germany	48 (44.4%)	11 (19.3%)	2 (28.6%)	61 (35.5%)
	Total	181 (42.3%)	59 (23.7%)	52 (44.8%)	292 (36.8%)
Male	Slovenia	13 (52.0%)	3 (11.1%)	2 (4.3%)	18 (18.2%)
	Spain	20 (64.5%)	12 (27.9%)	37 (63.8%)	69 (52.3%)
	Sweden	13 (31.7%)	8 (20.0%)	2 (6.9%)	23 (20.9%)
	Netherlands	7 (14.3%)	1 (2.5%)	1 (12.5%)	9 (9.3%)
	Germany	17 (25.4%)	3 (10.0%)	2 (33.3%)	22 (21.4%)
	Total	70 (32.9%)	27 (15.0%)	44 (29.7%)	141 (26.1%)

Logistic regression model for positive SCD including: RUN (LR[2df] = 74.0; P < .001), country (LR[4df] = 157.7; P < .001), age (LR[3df] = 4.9; P = .173), and sex (LR[2df] = 18.4; P < .001).

TABLE 6 Likelihood of a positive pre-screening result based on sex, initiative, age, and country

	Positive pre-screening		Negative pre-screening		Odds Ratio[b]	95% CI	P > |z|
	N	%	n	%			
Sex							
Female[a]	634	56.2	1041	60.6	1		
Male	486	43.0	660	38.4	1.11	(0.95-1.30)	0.19
Unknown	9	0.8	17	1.0	0.75	(0.33-1.74)	0.51
Initiative							
RUN 1 (WB)[a]	547	48.4	940	54.7	1		
RUN 2 (OHI)	235	20.8	426	24.8	1.09	(0.87-1.36)	0.45
RUN 3 (PC)	193	17.1	242	14.1	1.46	(1.15-1.85)	<0.01
RUN 4 (DC)	154	13.6	110	6.4	2.24	(1.70-2.95)	<0.01
Country							
Slovenia	359	31.8	533	31.0	2.10	(1.54-2.86)	<0.01
Spain	377	33.4	466	27.1	2.23	(1.64-3.02)	<0.01
Sweden	127	11.2	254	14.8	1.20	(0.86-1.68)	0.28
Netherlands	176	15.6	234	13.6	2.12	(1.54-2.91)	<0.01
Germany[a]	90	8.0	231	13.4	1		
Age category							
65-69 years[a]	406	36.0	829	48.3	1		
70-74 years	334	29.6	435	25.3	1.53	(1.26-1.85)	<0.01
75-79 years	235	20.8	298	17.3	1.61	(1.29-2.00)	<0.01
80-85 years	154	13.6	156	9.1	2.03	(1.56-2.65)	<0.01

[a]Baseline category.
[b]Estimates adjusted for all variables in the table obtained using a logistic regression model.

The results of the MMSE and SCD assessments seem to confirm this hypothesis, as we found that individuals being pre-screened in the OHI presented with higher MMSE scores and a larger proportion of individuals with SCD than those individuals pre-screened in the PC and DC initiatives. As a direct consequence, we do not expect all initiatives to be able to detect the same proportion of cases of prodromal AD or mild AD dementia. In fact, our results show that the proportion of individuals receiving a positive pre-screening result was quite different between the four initiatives, even when age and sex differences were adjusted for. This does not necessarily mean that some initiatives are more sensitive than others. A more likely explanation is that the profile of individuals undergoing each one of these initiatives and their background risks of dementia are quite different, as suggested by their MMSE scores. For instance, individuals with diabetes from DC initiative are more likely to have cognitive decline than same age-and-sex individuals participating in a web-based initiative. But these differences might occur even within the same strategy. We observed that for some reason the proportion of female participants was lower among individuals participating in the WB initiative in Spain than in other countries. In fact, the factors that induce someone to participate in these initiatives, like access to the internet in the WB initiative or access to tertiary care in the DC initiative, might differ not just between countries, but also within the same country (eg, rural vs urban areas).

As these factors change, the profile of participants in these initiatives also changes. Thus differences between participating countries (such as differing health systems, or geographical and social contexts) introduce within-RUN heterogeneity in the study results. Although this represents a challenge, this multi-site approach provides valuable information much needed to comprehend the potential of these pre-screening initiatives.[16] Based on these results, if we truly aim at improving patient engagement and promoting early diagnosis of prodromal AD and mild AD dementia, we advocate for a comprehensive pre-screening strategy that involves different initiatives tailored to different subpopulations. For the same reasons, there might be instances when some initiatives are preferred over the others. When planning to use these pre-screening tools to ascertain potential candidates to be enrolled in randomized clinical trials, we might want to favor population-based over patient-based initiatives, since they tend to identify patients at earlier stages of the disease.

During the current coronavirus disease 2019 (COVID-19) pandemic we have all experienced how the use of technologies can substantially ease the burden of government-imposed lockdowns. Not only has technology allowed us to keep in touch with family and friends, but more importantly telemedicine tools have been key to ensuring continuity of "non-essential" medical care, such as dementia care.[17] In this context, initiatives like the WB pre-screening, aimed at identifying

people at risk of dementia, avoiding face-to-face visits is particularly helpful.

It is important to highlight that these initiatives, apart from allowing for an early diagnosis among pre-screened individuals, help raise awareness of the problem at different levels. Thus, although the WB and OHI raise public awareness, the PC and DC initiatives reach out to primary care and tertiary care professionals who become aware of the importance of early diagnosis. In addition, we should bear in mind that not all individuals with a positive pre-screening result will be ultimately diagnosed with AD. The upcoming results of the validation studies of these pre-screening initiatives, based on the proportion of confirmed MCI and early AD diagnosis observed among those individuals with a positive result who undergo clinical evaluation in the participating memory clinics will help identify the strengths and weaknesses of these strategies.

Overall, the four patient engagement initiatives within MOPEAD project were able to identify four individuals at high risk of having prodromal AD or dementia for every 10 pre-screened individuals. Furthermore, our results show marked differences among participants of these pre-screening initiatives. These differences could explain the dissimilar observed proportion of individuals with positive result in each initiative. As we attempt to promote the early diagnosis of AD, the use of different but complementary pre-screening initiatives should help achieve this goal.

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