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Effects of Eligibility Criteria on Patient Selection and Treatment Implications from 10 Multidomain Dementia Prevention Trials: A Population-Based Study

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Prevention · Dementia · Ageing · Trials · Cardiovascular · Lifestyle · Guidelines

Abstract

Introduction: Dementia prevention trials have so far shown little benefit of multidomain interventions against cognitive decline. Recruitment strategies in these trials often centre around dementia risk or cardiovascular risk profile, but it is uncertain whether this leads to inclusion of individuals who may benefit most from the intervention. We determined the effects of eligibility criteria on the recruitment of potential trial participants in the general population. ***Methods:*** In a systematic search until January 1, 2022, we identified all published and ongoing large (≥500 participants), phase-3 multidomain trials for the prevention of cognitive decline or dementia. We applied trial eligibility criteria to 5,381 participants of the population-based Rotterdam Study (mean age: 72 years, 58% women), to compare participant characteristics, predicted risk of cardiovascular disease, and dementia risk, between trial eligible and ineligible persons. ***Results:*** We identified 10 trials, of which 5 had been published (DR's EXTRA, FINGER, preDIVA, MAPT, and HATICE) and 5 are ongoing (US-POINTER, MIND-CHINA, MYB, AgeWell.de, and J-Mint). Among all Rotterdam Study participants, eligibility across published trials ranged from 48% for MAPT to 87% for preDIVA, in line with original trial reports. Variability in eligibility was wider for ongoing trials, from 1% for US-POINTER to over 94% for MYB trial. Over 70% of trial eligible individuals are recommended preventive intervention in routine care based on their cardiovascular risk, similar for lipid-lowering (71%) and blood pressure-lowering treatment (73%). Ten-year risks of dementia were similar for eligible compared to ineligible individuals (12 vs. 11%). ***Conclusion:*** Multidomain dementia prevention trials fail to preferentially include those at the highest risk of dementia and mostly include individuals who qualify for interventions already on the basis of cardiovascular prevention guidelines. These findings call for better targeted enrolment of individuals for whom trial results can improve clinical decision-making.

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Introduction

In the past decade, several large dementia prevention trials have studied the efficacy of multidomain lifestyle interventions on cognition, but only one has shown a significant benefit on cognitive decline [1–5]. These largely disappointing findings inspired additional trials to refine their target population in order to detect potential benefits from lifestyle interventions on preventing cognitive decline and dementia [6, 7]. One of the most critical aspects of the design of these studies is the selection criteria for study participants. Given that Alzheimer's disease has a very long latency period (up to 20 years) from the onset of the neuropathological changes in the brain to the development of clinical symptoms, individuals to be included in the trials need to be carefully selected from the general population. They need to be at increased risk of dementia as well as be at a preclinical disease stage where the underlying neurodegenerative process can be reversed, halted, or at least significantly slowed. If either of those conditions is not satisfied, a potentially beneficial intervention might fail to show a significant effect in the context of a clinical trial, either due to lack of study power to detect such an effect or due to a too advanced stage of the underlying neurodegenerative process, when beneficial interventions are no longer effective.

Currently, the design of most of these trials is characterized by the recruitment of older persons with a high-risk profile for cognitive decline [7, 8], on the basis of the well-established role of cardiovascular risk factors in the pathophysiology of late-life dementia [9]. However, the premises underlying preferential inclusion of persons at high cardiovascular risk do not necessarily translate into improved dementia prevention, for three reasons.

Firstly, recent studies show that the accuracy of predicting the absolute, individualized risk of dementia based on cardiovascular risk factors is limited, casting doubt about the utility of this approach for identifying those persons who are at the highest risk of dementia and thus would be assumed to benefit most from a preventive intervention [10, 11]. Secondly, in the target population with below par cardiovascular health, people may already qualify for lifestyle modification and/or pharmaceutical preventive interventions on the basis of cardiovascular disease guidelines, regardless of their dementia risk [4]. Thirdly, a high (competing) risk of cardiovascular death may in fact lower one's lifetime dementia risk compared to persons with fewer cardiovascular risk factors and longer life expectancy. Therefore, preferential inclusion of those at the highest cardiovascular risk could lead to neglecting individuals for trials who may benefit most from intervention in terms of cognition.

Understanding the impact of these dynamics on trial populations is pivotal to inform future trial design and ensure representation of the proper target populations. In this study, we therefore aimed to characterize eligibility of older individuals from an unselected population for published and ongoing dementia prevention trials. We also determined the proportion of persons that qualified for preventive interventions according to the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) and the American College of Cardiology/American Heart Association (ACC/AHA) cardiovascular disease prevention guidelines [12, 13] and evaluated whether trial inclusion criteria optimally captured the population at high-dementia risk.

Materials and Methods

Search for Completed and Ongoing Dementia Prevention Trials

We conducted a literature review to identify published and ongoing phase-3 trials (SL and FJW) that aimed to assess the efficacy of multidomain lifestyle interventions on all-cause dementia or cognitive decline. The search included articles in the PubMed, Embase, Scopus, and Web of Science libraries, published between database inception and January 1, 2022. We additionally hand-searched for other potentially relevant publications in reference lists from identified papers, including a recent Cochrane review [14]. We searched grey literature and clinical trial registries to identify multidomain dementia prevention trials that are ongoing or recruiting participants. The full search string is presented in the online supplement (for all online suppl. material, see www.karger.com/doi/10.1159/000528120). We included trials if they met each of the following three criteria: [1] (anticipated) inclusion of at least 500 non-demented, community-dwelling older adults; [2] investigation of the efficacy of multidomain lifestyle interventions; and [3] cognitive decline or all-cause dementia as a (primary) outcome measure of interest. A minimum sample size of 500 persons was chosen for reasons of efficiency as well as capturing in more detail trials with expected greater precision. For each of the included trials, we summarized key characteristics, such as geographic location, entry criteria, intervention/comparison, duration of follow-up, and primary outcome. We further extracted inclusion and exclusion criteria and reported eligibility in the original trials.

Study Population for Application of Trial Eligibility Criteria

To evaluate for each of these trials, the number of eligible individuals in the general population, we applied the trial eligibility criteria to participants of the Rotterdam Study. This is a prospective, population-based cohort study of all residents aged 55 years and older who live in a geographically defined district of Rotterdam, the Netherlands [15]. Of 10,215 invited inhabitants at cohort inception in 1990, 7,983 (78%) agreed to participate in the baseline

examination. In 2000, the cohort was expanded with all residents who turned 55 or moved into the study area. Of the 4,472 invitees, 3,011 (67%) agreed to participate. Follow-up examinations take place every 4 years. For the current study, we used data obtained during the fourth round (2002–2003) of the first recruitment wave (n = 3,550) and the second round of the second recruitment wave (2003–2006; n = 2,468). We chose these rounds to maximize the amount of available data on relevant trial eligibility criteria and because recruitment of published prevention trials was closest to (calendar) time of these specific examination rounds. We excluded 624 participants who did not complete the interview and research centre visit and 11 participants who did not provide informed consent to access medical records and hospital discharge letters, leaving 5,381 participants (89.4%) for analyses.

Ascertainment Methods of Study Population Characteristics

Standardized assessment of anthropometrics of the study, including cardiovascular risk factors, gait, clinical disease manifestations, brain MRI, and use of medication, are described in the online supplement.

Assessment of Dementia

Participants were screened in-person for dementia at baseline and at subsequent centre visits with the Mini-Mental State Examination (MMSE) and the Geriatric Mental State Schedule organic level [16]. Those with an MMSE score <26 or a Geriatric Mental State Schedule score >0 underwent further investigation and an interview with next of kin, including the Cambridge Examination for Mental Disorders of the Elderly. The information from in-person screening was supplemented by data from the electronic linkage of the study database with medical records from all general practitioners and the regional institute for outpatient mental health care. In the Dutch health care system, the general practitioner serves as a "gate keeper" for referral to specialist care. The entire Dutch population is entitled to primary care that is covered by their (obligatory) health insurance. The Rotterdam Study cohort is thus continuously monitored for the detection of interval cases of dementia or cognitive impairment between centre visits. A consensus panel led by a consultant neurologist established the final diagnosis according to standard criteria for dementia (DSM-III-R).

Guideline Recommendations regarding Lipid-Lowering or Blood Pressure-Lowering Treatment

For each participant, we calculated the 10-year predicted risk for atherosclerotic cardiovascular (ASCVD) mortality following guidelines of the 2019 ESC/EAS guidelines and the 10-year predicted risk for hard ASCVD following guidelines of the 2019 ACC/AHA guidelines [12, 13]. As recommended by ESC/EAS, we used sex-specific Systematic Coronary Risk Evaluation (SCORE) equations for low-risk countries. For ACC/AHA guidelines, we used sex-specific Pooled Cohort Equations for white persons [17]. Over the years, various updates of these preventive cardiology guidelines have been published. To facilitate a direct comparison across all trials, we chose guideline versions that were closest in calendar years to the actual time periods for the majority of trials at time of study design or enrolment. For both lipid-lowering and blood pressure-lowering treatment, we defined treatment recommendations in accordance with ESC/EAS and ACC/AHA risk thresholds: no treatment, treatment considered, and treatment recommended [12, 13].

Statistical Analysis

Analyses presented in this paper are conducted in three steps and were all stratified by sex. Firstly, we determined eligibility of community-dwelling participants for each of the identified trials by applying relevant inclusion and exclusion criteria from those trials to the Rotterdam Study cohort. We compared key demographics and participant characteristics (age, sex, race, level of attained education, cardiovascular risk factors, MMSE, and memory complaints) of the original trial populations with those of the Rotterdam Study participants that were deemed eligible for each of the trials.

In the secondly step, we determined for each trial, the proportion of trial eligible persons in the Rotterdam Study cohort that would qualify for cardiovascular preventive treatment under the ESC/EAS guidelines. This includes lifestyle modification and also indications for lipid- or blood pressure-lowering treatment.

In the thirdly step, we determined whether eligibility criteria led to the recruitment of persons at the highest risk for dementia. Among the persons eligible for each of the trials, we calculated 10-year predicted risks of ASCVD mortality using coefficients from previously published SCORE equations and 10-year predicted risk of hard ASCVD using pooled cohort equations. In the absence of clinically established dementia predictive models, we determined 10-year risk of dementia and remaining risk of dementia until the age of 90 based on observed cumulative incidences within the Rotterdam Study cohort to account for competing death due to causes other than dementia [18]. The upper limit of 90 years was set in view of the maximum age of participants in the included trials. The estimates of the remaining risk of dementia thus reflect the cumulative incidence from age at trial entry to the age of 90 years. We then compared the individual risk estimates for ASCVD and dementia between eligible and ineligible persons for each trial separately.

We assessed the robustness of our findings through four sensitivity analyses. Firstly, we reanalysed preventive treatment qualifications among eligible and ineligible persons under 2019 ACC/AHA instead of ESC/EAS guidelines. Secondly, we recalculated the proportion of persons that qualified for preventive treatment under ESC/EAS that were free from a history of cardiovascular disease at study baseline. Thirdly, we used SCORE equations for older persons (SCORE-OP) to calculate cardiovascular risk among persons aged 70 years and older [19]. Fourthly, we recalculated 10-year and remaining dementia risk using the maximum observed age in this study (106 years for men and 102 years for women) rather than the earlier applied limit of 90 years. For data analysis, we used R, CRAN version 4.0.0, using the rms, etm, and cmprsk packages. Results have been reported to confirm with STROBE guidelines, and the corresponding checklist for cohort studies is available in the online supplement.

Results

Among 1,655 screened abstracts, we identified five completed and published dementia prevention trials with at least 500 community-dwelling persons: the Dose Responses to Exercise Training (DR's EXTRA) Study published in 2010 [20], the Finnish Geriatric Intervention

Table 1. Baseline characteristics for the overall Rotterdam Study cohort and according to their eligibility for published trials

	All participants	DR's EXTRA	preDIVA	FINGER	MAPT	HATICE
No. of participants within the trial entry age	5,381	4,108	1,769	5,381	3,042	4,346
No. of participants with complete data per trial to assess eligibility		3,979	1,769	4,927	711	3,736
No. of eligible participants		2,891	1,533	2,481	342	2,649
Eligibility in the Rotterdam Study	–	72.7%	86.7%	50.4%	48.1%	70.9%
Age, mean (SD)	72.3 (7.6)	68.6 (5.0)	73.8 (2.3)	70.2 (7.2)	74.9 (4.0)	74.0 (6.1)
Women, *n* (%)	3,111 (57.8)	1,700 (58.8)	864 (56.3)	1,690 (68.1)	183 (53.5)	1,534 (57.9)
Caucasian, *n* (%)	4,989 (96.6)	2,661 (97.0)	1,462 (97.7)	2,316 (97.5)	327 (98.2)	2,552 (97.7)
Educational attainment, *n* (%)						
Primary only	520 (9.7)	229 (7.9)	164 (10.7)	266 (10.7)	29 (8.5)	286 (10.8)
Lower	2,124 (39.4)	1,246 (43.1)	646 (42.1)	1,156 (46.6)	142 (41.5)	1,144 (43.2)
Further	1,475 (27.4)	856 (29.6)	471 (30.7)	660 (26.6)	132 (38.6)	796 (30.0)
Higher	669 (12.4)	406 (14.0)	158 (10.3)	272 (11.0)	36 (10.5)	309 (11.7)
Smoking, *n* (%)						
Never	1,655 (30.8)	896 (31.0)	409 (26.7)	858 (34.6)	109 (31.9)	768 (29.0)
Past	2,906 (54.0)	1,579 (54.6)	938 (61.2)	1,247 (50.3)	204 (60.0)	1,484 (56.0)
Current (%)	702 (13.0)	409 (14.1)	181 (11.8)	346 (13.9)	28 (8.2)	397 (15.0)
Systolic blood pressure, mm Hg	150 (21)	147 (20)	150 (21)	151 (20)	149 (19)	154 (20)
MMSE, median (IQR)	28 (26–29)	28 (27–29)	28 (27–29)	28 (27–29)	28 (27–29)	28 (27–29)
Memory complaints, *n* (%)	2,479 (46.0)	1,294 (44.8)	785 (51.2)	1,169 (47.1)	289 (84.5)	1,356 (51.2)
Diabetes, *n* (%)	711 (13.2)	355 (12.3)	200 (15.4)	300 (12.1)	38 (11.1)	423 (16.0)

SD, standard deviation; MMSE, Mini-Mental State Examination; IQR, interquartile range.

Study to Prevent Cognitive Impairment and Disability (FINGER) trial in 2015 [5], the Prevention of Dementia by Intensive Vascular care (preDIVA) trial in 2016 [4], the Multidomain Alzheimer Preventive Trial (MAPT) in 2017 [2], and the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial in 2019. From grey literature and clinical trial registries, we additionally included another five trials that are ongoing at the time of the search: the US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US-POINTER), a randomized controlled trial for Multimodal Intervention to Delay Dementia and Disability in China (MIND-CHINA), Maintain Your Brain-Trial (MYB), AgeWell.de, and the Japan-Multimodal Intervention Trial for Prevention of Dementia (J-Mint) [21–25]. A flowchart leading to the included studies is presented in online supplementary eFigure1. Detailed information on specific RCT eligibility criteria, study design, and outcomes is provided in online supplementary eTable 1.

Trial Eligibility

Characteristics of the general population sample from the Rotterdam Study are presented in Table 1. Participants excluded from the present study had a similar age (mean 72.4 years, SD 8.6 years) yet more often were women (67.2%) compared to the participants that were included in the analyses (mean age 72.3 years and 57.8% women). Due to narrow age entry criteria for preDIVA (70–78 years) and MAPT (≥70 years), relatively few Rotterdam Study participants could be further assessed for eligibility for these trials. Eligibility within this general population sample for published trials is shown in Table 1 and for ongoing trials in Table 2. Characteristics of eligible persons were largely similar to those of the participants included in the original trials [2–5, 20]. Eligibility across published trials ranged from 48.1% for MAPT up to 86.7% for preDIVA (Table 1), close to the estimates in the original publications (mean difference: 4.1% [range: 0.2–16.7%]). The difference was the largest for MAPT, which recruited primarily via memory clinics, with an eligibility of 64.8% in the trial source population compared to 48.1% in this general population cohort. Across the five published trials, 127 persons from the population-based sample (2.2%) were eligible for all five dementia prevention trials, whereas 1,028 (17.7%) persons were eligible for none of the five trials (Fig. 1).

Variability in trial eligibility was wider among ongoing trials than among published trials (online suppl. eTables 1, 2), ranging from 0.1% for US-POINTER to over 90% in the MIND-CHINA (92.7%), MYB (94.6%), and J-Mint trials (93.4%). Two persons (0.04%) were eligible for all five ongoing trials, whereas 130 (2.4%) were eligible for none of

Table 2. Baseline characteristics for the overall Rotterdam Study cohort and according to their eligibility for ongoing trials

	All participants	US-POINTER	MIND-CHINA	MYB trial	J-Mint	Agewell.de
No. of participants within the trial entry age	5,381	4,396	5,157	5,336	4,033	4,929
No. of participants with complete data per trial on eligibility criteria		4,146	4,071	3,891	4,025	3,430
No. of eligible participants		4	3,773	3,679	3,686	752
Eligibility in the Rotterdam Study		0.1%	92.7%	94.6%	93.4%	21.9%
Age, mean (SD)	72.3 (7.6)	73.9 (4.2)	69.2 (5.1)	68.6 (4.7)	73.3 (5.4)	69.0 (4.5)
Women, *n* (%)	3,111 (57.8)	4 (100)	2,108 (55.9)	2,045 (55.6)	1,949 (52.9)	587 (78.1)
Caucasian, *n* (%)	4,989 (96.6)	4 (100)	3,490 (97.3)	3,390 (97.1)	3,237 (97.9)	705 (96.7)
Educational attainment, *n* (%)						
Primary only	520 (9.7)	4 (100)	290 (7.6)	273 (7.4)	359 (10.1)	159 (21.1)
Lower	2,124 (39.4)	0 (0)	1,598 (42.4)	1,526 (41.4)	1,421 (40.8)	386 (51.3)
Further	1,475 (27.4)	0 (0)	1,122 (29.7)	1,051 (28.6)	1,014 (29.4)	152 (20.2)
Higher	669 (12.4)	0 (0)	556 (14.7)	545 (14.8)	403 (11.8)	55 (7.3)
Smoking, *n* (%)						
Never	1,655 (30.8)	1 (25.0)	1,103 (29.2)	1,058 (28.8)	981 (26.6)	252 (33.5)
Past	2,906 (54.0)	3 (75.0)	2,104 (55.8)	1,987 (54.0)	1,940 (52.6)	399 (53.1)
Current	702 (13.0)	0 (0)	551 (14.6)	548 (14.9)	441 (12.0)	101 (13.4)
Systolic blood pressure, mm Hg	150 (21)	150 (16)	148 (20)	147 (20)	151 (21)	155 (18)
MMSE, median (IQR)	28 (26–29)	28 (26–29)	28 (27–29)	28 (27–29)	28 (27–29)	28 (26–29)
Memory complaints, *n* (%)	2,479 (46.0)	3 (75.0)	1,719 (45.6)	1,609 (43.7)	1,729 (46.9)	368 (48.9)
Diabetes, *n* (%)	711 (13.2)	0 (0)	467 (12.4)	452 (12.3)	443 (12.0)	115 (15.3)

SD, standard deviation; MMSE, Mini-Mental State Examination; IQR, interquartile range.

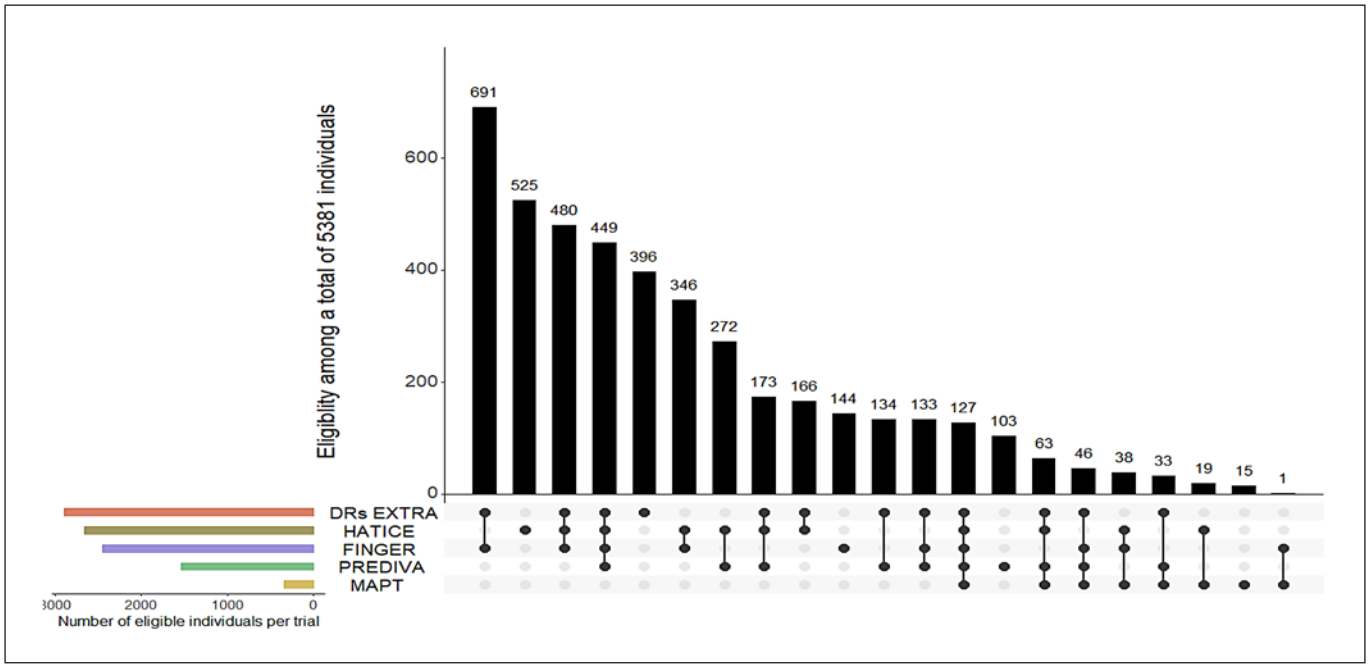

Fig. 1. Overlap in trial eligibility across published trials. Of all 5,381 participants in the Rotterdam Study cohort, 1,028 (17.7%) were not eligible for any of the trials, whereas only 127 individuals (2.2%) were eligible for all five trials. Each dot represents a mutually exclusive category. For example, 525 individuals were eligible only for HATICE. The FINGER and DR's EXTRA trials had the largest overlap in trial eligibility.

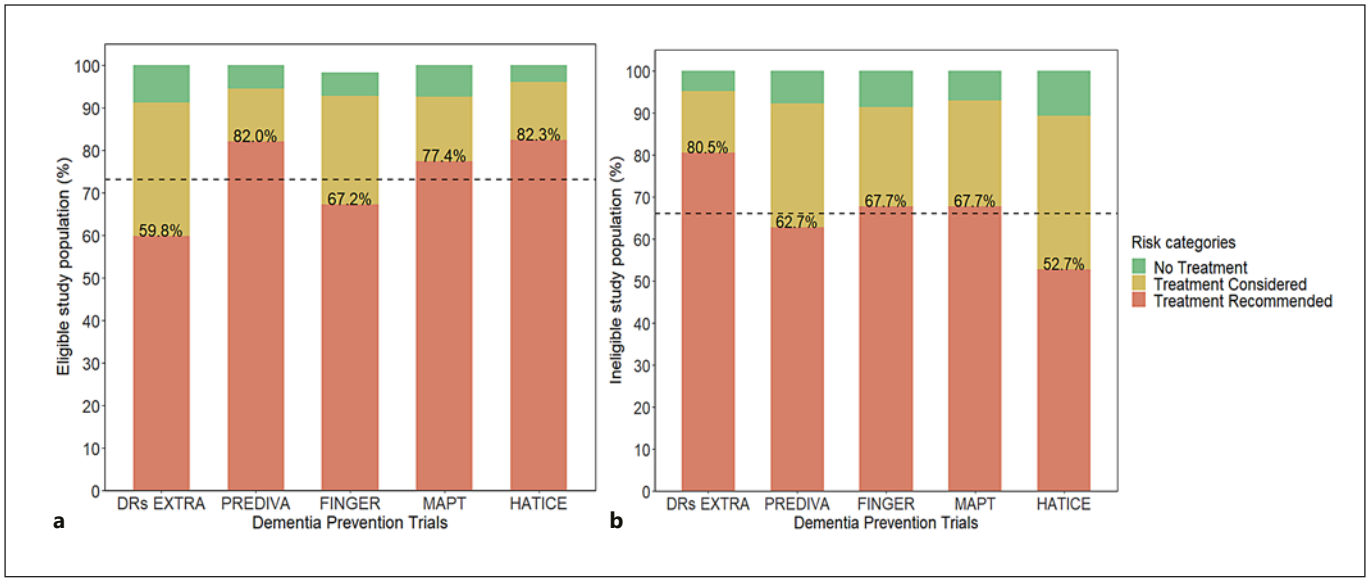

Fig. 2. Proportion of people in the general population who qualify for lipid-lowering treatment according to European guidelines for cardiovascular risk management, stratified by trial eligibility (panel **a**: eligible persons and panel **b**: ineligible persons). Dashed lines represent overall means of recommended cardiovascular preventive treatment.

Table 3. Ten-year risk of ASCVD in relation to risk of dementia, stratified by eligibility for each of the published dementia prevention trials

	10-year ASCVD risk [IQR]		10-year cumulative risk of dementia [95% CI]	Remaining risk of dementia until the age 90 [95% CI]
	fatal	fatal and non-fatal		
Eligible persons				
DR's EXTRA	5.7% [3.4–9.1]	18.3% [10.9–28.2]	8.0% [7.0–9.0]	23.6% [20.9–26.6]
preDIVA	9.3% [6.6–13.3]	28.3% [21.0–37.4]	13.2% [11.5–15.0]	22.3% [19.6–25.2]
FINGER	7.5% [4.1–13.3]	23.0% [12.5–27.6]	10.9% [9.6–12.1]	26.3% [23.6–29.3]
MAPT	9.2% [6.5–14.7]	28.9% [20.5–41.3]	8.6% [5.5–11.6]	15.6% [13.1–18.8]
HATICE	9.8% [6.3–15.9]	30.2% [20.4–45.4]	11.6% [10.4–12.8]	20.3% [17.7–23.3]
Pooled estimate	7.9% [4.8–13.0]	24.6% [15.3–36.9]	10.5% [9.9–11.1]	22.9% [20.3–25.9]
Ineligible persons				
DR's EXTRA	12.0% [7.3–18.9]	37.1% [24.3–53.3]	16.2% [14.9–17.6]	17.3% [9.4–15.0]
preDIVA	6.3% [3.4–14.3]	20.7% [11.0–44.0]	11.0% [10.0–12.0]	24.2% [21.5–27.2]
FINGER	8.2% [4.5–14.3]	26.8% [15.5–44.0]	12.1% [11.0–13.4]	19.3% [16.7–22.3]
MAPT	7.6% [4.1–13.7]	24.3% [13.5–41.1]	11.8% [10.9–12.7]	23.2% [20.6–26.2]
HATICE	5.3% [2.9–10.3]	17.3% [9.3–33.0]	11.6% [10.4–12.8]	27.7% [25.1–30.7]
Pooled estimate	7.8% [4.1–14.6]	25.4% [13.6–44.0]	12.4% [11.9–12.9]	22.4% [19.8–25.4]

ASCVD, atherosclerotic cardiovascular disease; IQR, interquartile range; CI, confidence interval.

these trials (online suppl. eFig. 2). Eligibility for US-POINTER was limited chiefly by the joint presence of a sedentary lifestyle and a poor diet or having a first-degree family member with significant memory impairment.

Indication for Preventive Cardiovascular Treatment

Overall, men more often qualified for lipid-lowering treatment than women (77.9 vs. 66.5%, p for difference <0.0001). Approximately 70% of all persons that were eligible for trial inclusion, qualified for pharmaceutical

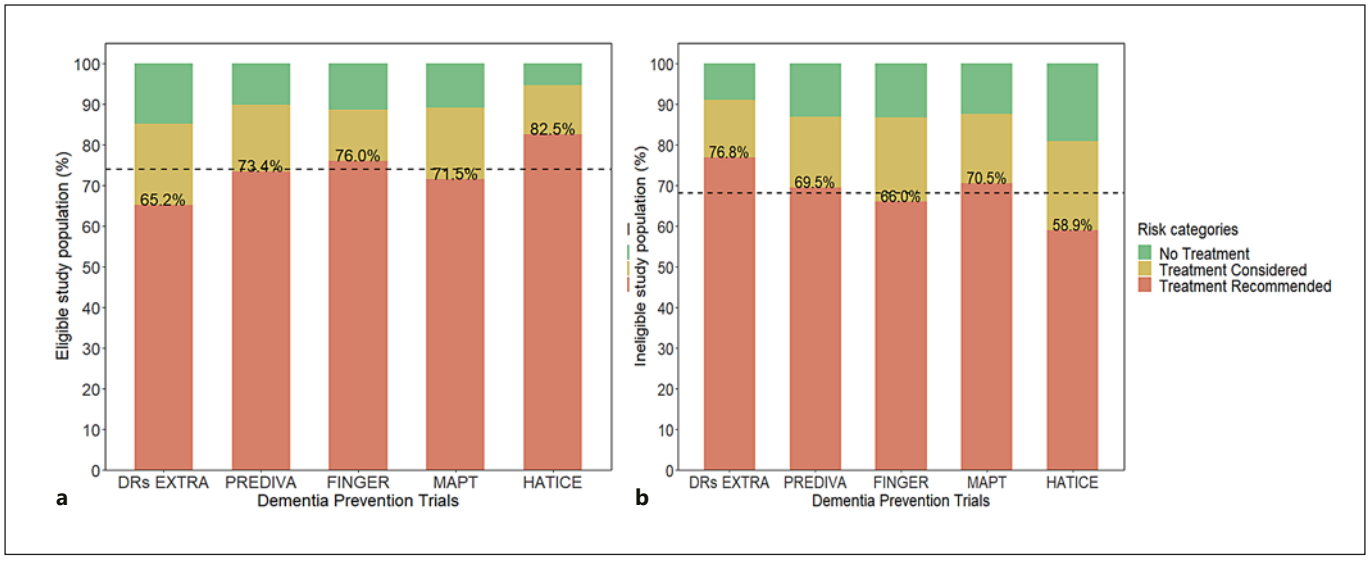

Fig. 3. Proportion of people in the general population who qualify for blood pressure-lowering treatment according to European guidelines for cardiovascular risk management, stratified by trial eligibility (panel **a**: eligible persons and panel **b**: ineligible persons). Dashed lines represent overall means of recommended cardiovascular preventive treatment.

preventive treatment with lipid-lowering medication (overall 71.0%, range: 59.8–82.6% Figure 2; ongoing trials presented in online suppl. eFig. 3). Recommendation for lipid-lowering treatment was higher for eligible compared to ineligible individuals in all trials, except for DR's EXTRA (indication across trials: 71.0% for eligible vs. 60.3% for ineligible persons; $p < 0.0001$; Fig. 2). Similarly for blood pressure-lowering treatment, 73.8% of trial eligible persons qualified for preventive treatment, somewhat more often as compared to ineligible individuals (68.5% $p < 0.0001$; Fig. 3).

Risk of Cardiovascular Disease and Dementia

Ten-year risk and remaining lifetime risk of dementia did not differ by trial eligibility (Table 3 and online suppl. eTable 4 for ongoing trials). In fact, in all but two trials, 10-year dementia risk among ineligible individuals exceeded that of eligible individuals. Median predicted 10-year risk of ASCVD was consistently higher than the 10-year risk of dementia for eligible as well as ineligible persons (Table 3 for published trials and online suppl. eTable 3 for ongoing trials). Women had lower predicted 10-year ASCVD risk than men (20.3 vs. 29.6%) but were at higher 10-year (10.4 vs. 9.4%) and remaining dementia risk (26.2 vs. 18.3%). Among all eligible persons at high 10-year ASCVD risk (>30%), absolute 10-year dementia risk was lower (15.1%), and mean dementia risk was even lower (7.5%) among those at lower 10-year ASCVD risk (≤30%). Predicted ASCVD risk indeed correlated positively with 10-year dementia risk but inversely with the remaining lifetime risk of dementia (online suppl. eFig. 4). In virtually all combinations of trial entry criteria, hard 10-year ASCVD risk was higher than the 10-year risk of dementia. However, several common trial eligibility criteria generally led to inclusion of persons at relatively high (remaining) dementia risk compared to low ASCVD risk, namely, female sex, lower education, difficulties managing finances, or medication. Conversely, a history of diabetes type 2, hypertension, or current smoking related to a relatively high ASCVD along with low (remaining) dementia risk (online suppl. eTable 4).

Sensitivity Analyses

When applying the ACC/AHA guideline criteria, the proportion of trial eligible persons that qualified for blood pressure-lowering treatment was largely similar compared to main analysis using ESC/EAS guidelines (70.9% vs. 73.8%). However, an even higher proportion of eligible persons qualified for lipid-lowering treatment under ACC/AHA compared to ESC/EAS guidelines (85.8 vs. 71.0%, online suppl. eFig. 5). Excluding people with a history of cardiovascular disease did not materially alter the proportion of ineligible persons that qualified for preventive treatment (60.3% vs. 59.8% under ESC/EAS

guidelines, and 75.6% vs. 75.7% under ACC/AHA guidelines). Using SCORE-OP equations, preventive treatment is to be considered or recommended in 94.1% all of those aged 70 years and older. Differences across trials in remaining risk of dementia became more pronounced when relaxing the upper age limit for remaining risk estimation from 90 to 106 years (online suppl. eTable 5).

Discussion

In this population-based sample, we found that up to 70% of older adults that are considered eligible for multidomain dementia prevention trials are already recommended lipid- or blood pressure-lowering treatment on the basis of cardiovascular disease prevention guidelines. Trials generally aimed to select persons at high risk of dementia, but ASCVD risk consistently outweighed their 10-year dementia risk across all studied trials. Moreover, the risk of dementia for ineligible persons was nearly identical, if not higher, to the risk for eligible persons. This means that the majority of trial recruitment strategies did not result in the selection of a segment of the population that is at markedly elevated dementia risk. Taken together, these findings demonstrate the challenge of obtaining equipoise in contemporary dementia prevention trials and provide guidance for more targeted trial inclusion of people considered to benefit most from preventive intervention.

Half of the dementia prevention trials that were included in this study were specifically designed to recruit a sample of persons at high risk of dementia based on the presence of cardiovascular risk factors [2, 5, 21, 23, 25]. Other trials used a more pragmatic design, with few inclusion criteria and enrolment based on age cut-offs, such as DR's EXTRA and preDIVA (also see online suppl. eTable 2) [4, 20]. Among persons at high risk of ASCVD in these trials, lifestyle advice is provided prior to preventive pharmaceutical intervention. However, these recommendations greatly overlap with those that should already have been provided according to preventive cardiology guidelines, such as suggestions or programs to improve exercise and diet. This raises ethical concerns whether stringent (lifestyle) interventions that are provided to both intervention as well as control groups in dementia prevention trials should not be offered to all older adults given their established beneficial effects on cardiovascular outcomes. Although trial interventions may help boost lifestyle adherence and pharmaceutical risk factor control compared to routine preventive practice, effects at the individual-level are generally small among older adults, and benefits from stringent interventions lessen over time, especially when trial interventions have been terminated [26]. A favourable combination of relatively low ASCVD risk and high (long-term) dementia risk was observed for eligibility criteria of the FINGER and DR's EXTRA trials. The FINGER study eligibility criteria included the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score, a validated score that predicts the risk of dementia in 20 years based on midlife cardiovascular risk factors, this score but also other validated indices may benefit trial design in successfully identifying individuals at high risk for dementia. Alternatively, this may be attributable in part to the inclusion of relatively young populations with a higher proportion of women, as compared to the other trials. Women have a higher long-term risk of dementia than men [27], due at least in part to longer life expectancy and survival free of ASCVD. Chronic exposure to cardiovascular risk factors among women that are below the absolute cardiovascular risk treatment threshold may gradually lead to the subclinical vascular brain injury that subsequently contributes to a high lifetime incidence of dementia. Indeed, we observed that women who were eligible for trial inclusion were at notably lower risk of ASCVD compared to men, hence less often qualified for cardiovascular preventive treatment than men.

Based on our findings, we propose three recommendations to improve the design of dementia prevention trials and to fulfil the potential of dementia prevention. Firstly, preventive efforts should ideally target persons who do not (yet) qualify for ASCVD prevention but are at high (lifetime) risk for dementia. Since mostly older adults already qualify for preventive cardiovascular treatment, this means we likely need to target younger populations to fulfil the potential of dementia prevention by means of cardiovascular risk factor management. This requires a new perspective on risk evaluation for trial recruitment, moving beyond a 5- or 10-year horizon for dementia to lifetime risk estimates. It is important to note that, in contrast to short-term risk, lifetime risk of dementia will mostly be inversely correlated to risk of ASCVD. Alternatively, trials may, for example, include younger persons genetically predisposed to develop dementia, in order to prevent cumulative exposure of cardiovascular risk factors over time that may catalyse dementia risk. As this will include participants that are possibly years prior to onset of symptoms, further development of validated markers of brain injury as a proxy

for clinical dementia is urgently required to increase the feasibility of conducting trials in younger populations with lower age-specific incidences of dementia. This could lead to the inclusion of individuals with accelerated rates of cognitive decline compared to the general population in order for sufficient dementia cases to develop during the study follow-up period, to allow for adequate power to detect a beneficial effect if one exists. Secondly, trialists could aim specifically for persons with subclinical brain disease, or risk factors that are deemed more specific to dementia than ASCVD, such as hearing impairment and social isolation. Such strategies could provide benefit on top of current routine cardiovascular preventive interventions [28]. Thirdly, to fulfil the potential of dementia prevention, a paradigm shift may be needed, away from treatment of the individual to treatment of the entire population. Confirming Geoffrey Rose's preventive paradox, this has already been shown to apply for the prevention of cardiovascular disease. Modelling studies show a modest 11% incidence reduction if all individuals at very high risk would be identified and treated perfectly compared to a 25–50% incidence reduction through population-wide preventive interventions [29].

Although we believe our findings can guide future trial design, several limitations need to be taken into account. Firstly, of approximately 45 unique trial criteria, there were two for which we had not systematically collected data (i.e., end-stage renal disease and bariatric procedures). However, prevalence of these conditions is less than 1% [30], and incorporating these criteria would have likely led to a higher share of participants already qualifying for cardiovascular treatment. Secondly, baseline recruitment for this study was between 2002 and2006. Although this aligns with the recruitment periods for published prevention trials, population-level risk factor control has improved, potentially further reducing the number of persons at high risk of dementia who remain untreated. Thirdly, although analyses with SCORE equations for Older Persons (SCORE-OP) yielded results similar to using the cardiovascular preventive guidelines, we may have overestimated real-world preventive practice for older adults with limited life expectancy in whom preventive intervention is discontinued, or in whom health care priorities are set otherwise. Fourthly, guidelines for primary prevention may not be fully applicable to some trial participants with a history of ASCVD. However, analyses among persons free of ASCVD yielded nearly identical results. Fifthly, the Rotterdam Study population is predominantly white (>95%), and results may not apply to other groups of the population. Finally, we note that various environmental factors (e.g., levels of air pollution, dietary habits, etc.), local health care structure, or the genetic diversity of this specific population might limit the applicability of the present findings to other populations**.** Strengths of this study include a high response rate and the meticulous assessment of a wide range of variables, which allowed a head-to-head comparison of the characteristics and prognosis from persons in- and excluded by published and ongoing dementia prevention trials.

In conclusion, 70% of the target population of contemporary multidomain dementia prevention trials already qualify for preventive interventions following international prevention guidelines. Dementia risk was nearly identical between trial eligible and ineligible persons. These findings call for better targeted enrolment of individuals for whom trial results can in fact improve clinical decision-making.

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Statement of Ethics

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, licence number 1071272-159521-PG). Written informed consent was obtained from all participants.

Conflict of Interest Statement

Dr Leening reports speaker fees from Sanofi-Genzyme Europe and serves on an advisory board for Boehringer Ingelheim; both unrelated to the submitted work. All other authors report no disclosures.

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Author Contributions

SL: data curation, formal analysis, investigation, methodology, visualization, writing – original draft, and writing – review and editing. FJW: conceptualization, investigation, methodology, writing – original draft, and writing – review and editing. JP: data curation, investigation, methodology, and writing – review and editing. MK: investigation, methodology, and writing – review and editing. MJGL: conceptualization, investigation, methodology, and writing – review and editing. MKI: investigation, methodology, writing – original draft, and writing – review and editing. MAI: conceptualization, funding acquisition, project administration, investigation, methodology, writing – original draft, and writing – review and editing.

Data Availability Statement

The datasets generated and/or analysed during the current study are not publicly available due to legal and ethical restraints but are available upon reasonable request. Requests can be directed to secretariat.epi@erasmusmc.nl or visit the following website for more information http://www.ergo-onderzoek.nl/wp/contact. Sharing of individual participant data was not included in the informed consent of the study, and there is a potential risk of revealing participants' identities as it is not possible to completely anonymize the data.

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