Determinants, MRI correlates, and prognosis of mild cognitive impairment: The Rotterdam Study

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ABSTRACT

Mild cognitive impairment (MCI) marks a transitional stage between healthy aging and dementia, but the understanding of MCI in the general population remains limited. We investigated determinants, MRI-correlates, and prognosis of MCI within the population-based Rotterdam Study. Firstly, we studied age, *APOE*-ε4 carriership, waist circumference, hypertension, diabetes mellitus, total and HDL-cholesterol levels, smoking, and stroke as potential determinants of MCI. Determinants were assessed cross-sectionally at baseline (2002-2005) and up to 7 years prior to baseline (1997-2001). Secondly, we compared volumetric, microstructural, and focal MRI-correlates in persons with and without MCI. Thirdly, we followed participants for incident dementia and mortality until 2012. Out of 4,198 participants, 417 had MCI, of whom 163 amnestic and 254 non-amnestic MCI. At baseline, older age, *APOE*-ε4 carriership, lower total cholesterol levels, and stroke were associated with MCI. Additionally, lower HDL-cholesterol levels and smoking were related to MCI when assessed 7 years prior to baseline. Persons with MCI, particularly those with non-amnestic MCI, had larger white matter lesion volumes, worse microstructural integrity of normal-appearing white matter, and a higher prevalence of lacunes, compared to cognitively healthy participants. MCI was associated with an increased risk of dementia (hazard ratio (HR) 3.98, 95% confidence interval (CI) 2.97;5.33), Alzheimer's disease (HR 4.03, 95% CI 2.92;5.56), and mortality (HR 1.54, 95% CI 1.28;1.85). In conclusion, we found that several vascular risk factors and MRI-correlates of cerebrovascular disease were related to MCI in the general population. Participants with MCI had an increased risk of dementia, including Alzheimer's disease, and mortality.

INTRODUCTION

Although the etiology of dementia is largely unknown, it is well established that neuropathology related to dementia slowly accumulates over decades. Consequently, identifying persons at a higher risk of dementia could postpone or even prevent dementia by timely targeting modifiable risk factors.[1] In this light, mild cognitive impairment (MCI) has been identified as the transitional stage between normal aging and dementia. Thus far, several studies have focused on identifying determinants, magnetic resonance imaging (MRI)-correlates, and prognosis of MCI. Various studies have established the role of amyloid pathology in MCI, but emerging evidence also implicates vascular factors as risk factors for MCI.[2-4] However, findings on determinants, MCI-correlates, and prognosis of MCI vary greatly due to differences in study populations, definitions of MCI, and determinants under investigation.[2, 5-11] Studying MCI in the general population may strengthen previous findings on determinants and prognosis of MCI. More importantly, clinical studies may suffer from referral bias and reverse causality. In the general population referral bias is less present and investigating determinants years before MCI could overcome the problem of reverse causality.

In the population-based Rotterdam Study we investigated determinants, MRI-correlates, and prognosis of MCI. Firstly, we focused on several vascular risk factors that were measured not only cross-sectionally, but also up to 7 years prior to diagnosis of MCI. Secondly, we investigated the relation between MCI and volumetric, microstructural, and focal imaging markers. Thirdly, we followed participants over a period of 9 years to determine the risk of incident dementia, Alzheimer's disease, and mortality.

METHODS

Setting and study population

The Rotterdam Study is a prospective population-based cohort that started in 1990. Inhabitants, aged 55 years and older, of Ommoord, a district of Rotterdam, the Netherlands were invited to participate in the study.[12] Out of 10,215 invited inhabitants, 7,983 (78%) agreed to participate. In 2000, this cohort was extended with 3,011 participants (67% of invitees) who had become 55 years of age or had moved into the district since the start of the study. Every 4 years, participants are re-invited to undergo home interviews and various examinations at the research center.[12]

Between 2002-2005, which was the fourth examination round of the original cohort and the second examination round of the extended cohort, an extensive neuropsychological test battery was implemented in the Rotterdam Study.[12] Given that extensive neuropsychological testing is required to assess MCI, 2002-2005 was set as baseline for MCI screening in our study. Of the 6,061 study participants that underwent examinations

between 2002-2005, 192 participants were excluded because they were demented, 67 because they were not sufficiently screened for dementia, and another 250 participants because they did not answer the questions regarding subjective cognitive complaints. An additional 1,354 participants were excluded because they missed one or more cognitive test scores or had unreliable test scores. Eventually, 4,198 persons were eligible to participate in this study. Because MRI was implemented from 2005 onwards,[13] only a random subset of 697 out of 4,198 persons underwent MRI, which was on average 1.01 years (0.46 standard deviation (SD)) after MCI screening. Persons with cortical infarcts were excluded (N=15) as tissue loss and gliosis surrounding cortical infarcts may cause unreliable white matter lesion segmentations. Eventually, 682 participants were included in the analyses of MRI-correlates.

Determinants of MCI and other measurements

Determinants of MCI were selected based on biological plausibility and literature on established risk factors of dementia.[14-18] Educational level was assessed at study entry by interview and categorized into seven groups: primary education only or primary education with an unfinished higher education, lower vocational education, lower secondary education, intermediate vocational education, general secondary education, higher vocational education, and university. Since educational level was required for assessment of the MCI diagnosis, we imputed missing values for education (1.8%) based on age and sex.

Information on *APOE* genotype was obtained using polymerase chain reaction on coded DNA samples without knowledge of MCI diagnosis. This method has been described in detail previously.[19, 20] *APOE*-ε4 carrier status was defined as carrier of one or two ε4 alleles. Waist circumference was measured in centimeters at the level midway between the lower rib margin and the iliac crest, with participants in standing position without heavy outer garments and with emptied pockets while breathing out gently. Blood pressure was measured in sitting position on the right arm and calculated as the average of two measurements using a random-zero sphygmomanometer. Hypertension was defined as a blood pressure ≥140/90 mmHg or use of blood pressure lowering medication, prescribed for the indication of hypertension. Diabetes mellitus was defined as a fasting serum glucose level ≥7.0 mmol/L, non-fasting serum glucose level ≥11.1 mmol/L, or use of anti-diabetic medication. Serum glucose, total cholesterol, and HDL-cholesterol levels were acquired by an automated enzymatic procedure (Boehringer Mannheim System). Smoking habits were assessed by interview and categorized as current, former, and never smoking. At study entry, history of stroke was assessed using home interviews and confirmed by reviewing medical records. After entering the Rotterdam Study, participants were continuously followed-up for stroke through automatic linkage of general practitioner files with the study database. For

potential strokes, additional information was collected from hospital, nursing home, and general practitioner records. An experienced neurologist adjudicated the strokes using standardized definitions, as described in detail previously.[21]
Apart from educational level and *APOE*-ε4 carrier status, all measurements were assessed at each examination round of the Rotterdam Study. We used the measurements that were assessed at the baseline of this study (2002-2005), and the measurements that were assessed at the previous examination round, which was up to 7 years (mean 4.4 years, SD 0.55) prior to baseline (1997-2001) (**Supplementary Figure 1**).

Assessment of MCI

MCI was defined using the following criteria: 1) presence of subjective cognitive complaints, 2) presence of objective cognitive impairment, and 3) absence of dementia.
Subjective cognitive complaints were evaluated by interview. This interview included three questions on memory (difficulty remembering, forgetting what one had planned to do, and difficulty finding words), and three questions on everyday functioning (difficulty managing finances, problems using a telephone, and difficulty getting dressed). Subjective cognitive complaints were scored positive when a subject answered "yes" to at least one of these questions. We assessed objective cognitive impairment using a cognitive test battery comprising letter-digit substitution task, Stroop test, verbal fluency test, and 15-word verbal learning test based on Rey's recall of words.[22] To obtain more robust measures, we constructed compound scores for various cognitive domains including memory function, information-processing speed, and executive function.[22, 23] Briefly, compound score for memory was calculated as the average of Z-scores for the immediate and delayed recall of the 15-word verbal learning test. For information processing speed averaged Z-scores for the Stroop reading and Stroop colour-naming subtask and the letter-digit substitution task were used. Finally, executive function included Z-scores of the Stroop interference subtask, the letter-digit substitution task, and the verbal fluency test. We classified persons as cognitively impaired if they scored below 1.5 SD of the age and education adjusted means of the study population. We subsequently classified the MCI subtypes amnestic and non-amnestic MCI. Amnestic MCI was defined as persons with MCI who had an impaired test score on memory function (irrespective of other domains). Non-amnestic MCI was defined as persons with MCI having normal memory function, but an impaired test score on executive function or information-processing speed.

Brain MRI and post-processing

We performed a multisequence MRI protocol on a 1.5-Tesla scanner (GE Healthcare). The sequences in the imaging protocol consisted of three high resolution axial scans, i.e., a T1-weighted sequence (slice thickness 1.6 mm, zero-padded to 0.8), a proton

density-weighted sequence (slice thickness 1.6 mm), and a fluid-attenuated inversion recovery (FLAIR) sequence (slice thickness 2.5 mm).[13] For cerebral microbleed detection, we used a custom-made accelerated three-dimensional T2*-weighted gradient-recalled echo (3D T2* GRE (slice thickness 1.6 mm, zero-padded to 0.8).[24] For diffusion tensor imaging scans we used a 2D acquisition and EPI readout (slice thickness for DTI was 3.5 mm). Maximum b-value was 1000 s/mm^2 in 25 non-collinear directions (number of excitations (NEX)=1) and one volume was acquired without diffusion weighting (b-value= 0 s/mm^2).

We used an automated tissue segmentation, including conventional k-nearest-neighbor brain tissue classifier extended with white matter lesion (WML) segmentation,[25] to segment scans into grey matter volume, white matter volume, WML volume, cerebrospinal fluid, and background. Total brain volume was defined as the sum of total grey matter volume, white matter volume, and WML volume. Hippocampal volume was determined using an automated method, as described extensively before.[26]

The segmentation was brought to the DTI image space using boundary based registration performed on the white matter segmentation,[27] the b=0 and T1-weighted images.

Diffusion data was pre-processed using a standardized processing pipeline.[28] In short, DTI data was corrected for subject motion and eddy currents by affine co-registration of the diffusion weighted volumes to the b=0 volume, including correction of gradient vector directions. Diffusion tensors were estimated using a non-linear Levenberg Marquadt estimator, available in ExploreDTI.[29] Global fractional anisotropy (FA) and mean diffusivity (MD), measures of microstructural integrity, were computed from the estimated tensor images over the entire normal-appearing white matter in each subject. The final registration result of each scan was checked visually for errors.[30, 31] Partial volume effects and presence of multiple white matter fibre orientation within a voxel were thus minimized. Sixteen subjects had to be excluded from the white matter microstructural integrity analyses due to scanning artifacts or excessive motion. FA and MD were standardized to echo time (TE) values, because TE was not constant for all participants.

All scans were rated by 1 of 5 trained research-physicians to determine presence of microbleeds and lacunes of presumed vascular origin.[32] Microbleeds were rated as focal areas of signal loss, on 3D T2* Gradient Recalled Echo-weighted MR imaging. Lacunes were rated on FLAIR, proton-density-weighted and T1-weighted sequences, and were defined as focal lesions ≥3mm and <15mm in size, with the same signal intensity as cerebrospinal fluid on all sequences and a hyperintense rim on the FLAIR (when located supratentorially).[33] Infarcts showing involvement of grey matter were classified as cortical infarcts.

Assessment of dementia

Participants were screened for dementia at baseline and at follow-up examinations using a three-step protocol. Screening was done using the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS) organic level.[34, 35] Screen-positives (MMSE <26 or GMS organic level >0) subsequently underwent an examination and informant interview with the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX).[36] During this interview, more information on functional status and cognitive performance was collected. Participants who were suspected of having dementia underwent extra neuropsychological testing if necessary. Additionally, for persons not visiting the research center, the total cohort was continuously monitored for dementia through computerized linkage of the study database and digitized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. When information on neuroimaging was required and available, it was used for decision making on the diagnosis. In the end, a consensus panel, led by a neurologist, decided on the final diagnosis in accordance with standard criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)) and Alzheimer's Disease (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)).[37, 38] Follow-up for incident dementia was complete until January 1st, 2012.

Assessment of mortality

Deaths were continuously reported through automatic linkage with general practitioner files. In addition, municipal health records were checked bimonthly for information on vital status. Information about cause and circumstances of death was obtained from general practitioner and hospital records.[39] Follow-up for mortality was complete until January 1st, 2012.

Statistical analysis

Firstly, we examined whether risk factors of dementia were related to MCI using multivariate logistic regression models adjusted for age and sex cross-sectionally. Since vascular risk factors often correlate,[17] we estimated the independent effect of each risk factor by including all risk factors into the same model. Age was included per 5 year increase into the model and waist circumference, total and HDL-cholesterol levels were included per SD increase into the model. Persons with missing values were excluded from these analyses. We investigated whether excluded persons had different characteristics than persons who were included in the analysis using Univariate Analysis of Variance, adjusting for age and sex where appropriate. The same models as in the cross-sectional analysis were used to examine the relation with risk factors assessed

up to 7 years prior to MCI diagnosis. Secondly, we used linear and logistic regression to investigate the relation of MCI with volumetric markers (i.e., total brain volume, hippocampal volume, WML volume), microstructural integrity markers (i.e., mean FA, MD) and focal markers (i.e, cerebral microbleeds, lacunes) of brain pathology on MRI cross-sectionally. Hippocampal volume was studied as the mean of the left and right hippocampal volume. WML was log-transformed due to the skewed distribution. Volumetric and microstructural measures were modeled continuously. Microbleeds and lacunes were dichotomized into present versus absent. These analyses were adjusted for age and sex (model 1), and additionally for *APOE*-ε4 carriership, waist circumference, hypertension, diabetes mellitus, total and HDL-cholesterol levels, and smoking (model 2). In model 2 we investigated whether irrespective of the presence of vascular risk factors, persons with MCI had more volumetric, microstructural, and focal changes in the brain compared to cognitively healthy participants. Analyses of volumetric and microstructural integrity measures were also adjusted for intracranial volume. In addition we performed a sensitivity analysis for the imaging correlates, excluding participants who became demented in the period between MCI screening and MRI scanning (N=12). Thirdly, we used Cox proportional hazards to study the association between MCI and risk of dementia, Alzheimer's disease, and mortality longitudinally. These models were adjusted for the same determinants as described in model 2 but with addition of prevalent stroke and educational level. All analyses were repeated investigating the amnestic and non-amnestic MCI subtypes separately. Analyses were performed using statistical software package SPSS 20.0, using an α-value of 0.05.

RESULTS

Characteristics of the study population are presented in **Table 1**. Out of 4,198 participants, 417 (9.9%) had MCI. Of these, 163 had amnestic MCI and 254 had non-amnestic MCI. Missing values for determinants of MCI occurred in 268 participants (6.4%) in 2002-2005 (baseline) and in 615 participants (14.6%) in 1997-2001. Participants excluded from the baseline analyses were more often female, suffered more from hypertension, and had a larger waist circumference than participants included in the analyses. Participants excluded due to missing data in 1997-2001 were also more often female and more often hypertensive but had lower cholesterol levels than participants included in our analyses (**Supplementary Table 1**).

At baseline, older age (odds ratio (OR) per 5 year increase in age 1.20, 95% confidence interval (CI) 1.11;1.29), *APOE*-ε4 carriership (OR 1.26, 95% CI 1.00;1.59), lower total cholesterol levels (OR 0.87, 95% CI 0.78;0.98), and stroke (OR 2.12, 95% CI 1.40;3.19) were independently related to MCI (**Table 2**). Male gender and *APOE*-ε4

carriership were only related to amnestic MCI, whereas older age and lower total cholesterol levels were only related to non-amnestic MCI.

Older age (OR per 5 year increase in age 1.18, 95% CI 1.11;1.29), *APOE*-ε4 carriership (OR 1.35, 95% CI 1.06;1.72), lower HDL-cholesterol levels (OR 0.86, 95% CI 0.75;0.98), current smoking (OR 1.49, 95% CI 1.06;2.09) and prevalent stroke (OR 2.50, 95% CI 1.48;4.23) were related to MCI when assessed up to 7 years (mean 4.4 years, SD 0.55) prior to MCI diagnosis (**Table 3**). *APOE*-ε4 carriership and former and current smoking were related to amnestic MCI, whereas older age and lower HDL-cholesterol levels were related to non-amnestic MCI.

Out of 682 participants with MRI scanning, 49 screened positive for MCI. Participants with MCI, particularly those with non-amnestic MCI, had larger WML volumes compared to cognitively healthy participants (mean difference in log-transformed WML volume: 0.36, 95% CI 0.05;0.68). Persons with non-amnestic MCI also had worse microstructural integrity of normal-appearing white matter after adjustments for cardiovascular risk (mean difference in mean FA: -0.007, 95% CI -0.014;-0.001, mean difference in mean MD: 0.013, 95% CI 0.001;0.024) (**Table 4**, model II). As for focal markers of vascular brain pathology, microbleeds were more frequent in persons with MCI, however this association was not significant. Lacunes however, were more frequent in participants with MCI, again particularly in those with non-amnestic MCI (age and sex adjusted OR 3.16, 95% CI 0.98;10.19) (**Table 4**). MRI scanning was performed on average 1.0 years (SD 0.46) after MCI screening. During this time-interval, 12 of 682 participants who underwent MRI were diagnosed with dementia. Out of these, 6 were initially screened as having MCI. Excluding participants with dementia at time of MRI scanning did not change our results (data not shown).

During 24,934 person-years of follow-up, 215 participants developed incident dementia, of whom 177 had Alzheimer's disease. During 29,096 persons-years of follow-up, 827 persons died. Participants with MCI had an increased risk of dementia (age and sex adjusted hazard ratio (HR) 3.98, 95% CI 2.97;5.33) (**Table 5**). The risk of dementia was especially increased in persons with amnestic MCI (HR 6.89, 95% CI 4.74;10.01), but was also increased in persons with non-amnestic MCI (HR 2.65, 95% CI 1.79;3.92). Results were similar for Alzheimer's disease. We found that participants with MCI also had an increased risk of mortality (HR 1.54, 95% CI 1.28;1.85) (**Table 5**). These results did not change across MCI-subtypes and additional adjustments did not change our results.

Table 1. Characteristics of the study population

	Examinations at baseline 2002-2005		Examinations before baseline 1997-2001	
	No MCI N=3,781	**MCI N=417**	**No MCI[a] N=3,730**	**MCI[a] N=401**
Age, years	71.5 (7.1)	73.5 (7.5)	67.1 (7.0)	68.9 (7.4)
Females	58.2%	52.0%	58.1%	51.1%
APOE-ε4 carrier	26.2%	29.7%	26.2%	30.8%
Educational level				
Primary education	16.8%	24.8%	16.4%	23.8%
Lower vocational education	20.2%	22.4%	20.3%	22.5%
Lower secondary education	17.5%	9.2%	17.6%	9.4%
Intermediate vocational education	26.7%	28.2%	26.8%	28.6%
General secondary education	4.6%	1.9%	4.7%	2.0%
Higher vocational education	12.7%	11.4%	12.7%	11.6%
University	1.6%	1.9%	1.6%	2.0%
Waist circumference, cm	93.4 (11.8)	94.6 (12.4)	93.0 (11.5)	94.1 (11.9)
Hypertension	80.6%	83.0%	65.2%	70.9%
Diabetes mellitus	14.1%	19.2%	8.3%	9.6%
Cholesterol, mmol/l	5.65 (1.00)	5.43 (0.96)	5.84 (0.97)	5.75 (0.90)
HDL-cholesterol, mmol/l	1.46 (0.40)	1.41 (0.40)	1.40 (0.39)	1.32 (0.36)
Smoking				
Former	55.1%	55.6%	50.4%	50.6%
Current	15.1%	17.5%	19.0%	23.4%
Stroke	3.4%	8.2%	2.0%	5.0%
MRI imaging markers[b]				
Total brain volume, ml	923.9 (89.6)	906.3 (119.9)	NA	NA
Hippocampal volume, ml	3.0 (0.3)	3.0 (0.4)	NA	NA
White matter lesions, ml	3.5 (2.0-6.5)	4.5 (2.6-12.4)	NA	NA
Fractional anisotropy	0.35 (0.02)	0.34 (0.02)	NA	NA
Mean diffusivity, 10^{-3} mm^2/sec	0.77 (0.05)	0.79 (0.05)	NA	NA
Cerebral microbleeds	20.9%	28.6%	NA	NA
Lacunes	5.7%	16.3%	NA	NA

[a]MCI as assessed at baseline (2002-2005) [b]MR imaging was performed in a randomly selected subset (N=682). Continuous variables are presented as means (standard deviations) and categorical variables as percentages. White matter lesions are presented as median (interquartile range).

Abbreviations: MCI=mild cognitive impairment, N=number of participants, *APOE*=apolipoprotein E, HDL=high-density lipoprotein.

Table 2. Associations between risk factors of dementia and MCI at baseline (cross-sectional).

	MCI	Amnestic MCI	Non-amnestic MCI
	Odds ratio (95% CI) n/N 389/3,541	**Odds ratio (95% CI) n/N 154/3,541**	**Odds ratio (95% CI) n/N 235/3,541**
Age, per 5 years	1.20 (1.11;1.29)	1.04 (0.92;1.17)	1.30 (1.19;1.43)
Females	0.91 (0.70;1.17)	0.66 (0.45;0.98)	1.11 (0.80;1.54)
APOE-ε4 carrier	1.26 (1.00;1.59)	1.43 (1.01;2.02)	1.17 (0.86;1.58)
Waist circumference, per SD	1.04 (0.92;1.18)	1.03 (0.84;1.25)	1.05 (0.90;1.24)
Hypertension	0.94 (0.70;1.25)	1.03 (0.66;1.59)	0.88 (0.61;1.28)
Diabetes mellitus	1.24 (0.93;1.65)	1.44 (0.94;2.20)	1.11 (0.77;1.59)
Cholesterol, per SD	0.87 (0.78;0.98)	0.94 (0.79;1.11)	0.84 (0.73;0.97)
HDL-cholesterol, per SD	0.94 (0.83;1.06)	1.02 (0.84;1.23)	0.88 (0.75;1.04)
Smoking			
Former	0.96 (0.74;1.25)	1.08 (0.71;1.66)	0.90 (0.65;1.25)
Current	1.21 (0.86;1.70)	1.37 (0.81;2.31)	1.13 (0.73;1.74)
Stroke	2.12 (1.40;3.19)	2.68 (1.51;4.76)	1.78 (1.04;3.03)

Values represent odds ratios and 95% confidence intervals, adjusted for all other risk factors.
Abbreviations: MCI=mild cognitive impairment, CI=confidence interval, n=number of cases, N=number of controls, APOE=apolipoprotein E, SD=standard deviation, HDL=high-density lipoprotein.

Table 3. Associations between risk factors of dementia, assessed 7 years prior, and MCI.

	MCI	Amnestic MCI	Non-amnestic MCI
	Odds ratio (95% CI) n/N 348/3,235	**Odds ratio (95% CI) n/N 140/3,235**	**Odds ratio (95% CI) n/N 208/3,235**
Age, per 5 years	1.18 (1.11;1.29)	1.08 (0.95;1.23)	1.25 (1.13;1.38)
Females	0.93 (0.71;1.21)	0.75 (0.50;1.11)	1.08 (0.77;1.51)
APOE-ε4 carrier	1.35 (1.06;1.72)	1.54 (1.08;2.22)	1.23 (0.90;1.69)
Waist circumference, per SD	1.02 (0.90;1.16)	1.02 (0.84;1.24)	1.03 (0.87;1.21)
Hypertension	1.17 (0.90;1.52)	1.00 (0.68;1.45)	1.33 (0.94;1.87)
Diabetes mellitus	1.05 (0.72;1.54)	0.87 (0.46;1.62)	1.16 (0.73;1.84)
Total cholesterol, per SD	0.95 (0.85;1.07)	0.94 (0.78;1.12)	0.96 (0.83;1.11)
HDL-cholesterol, per SD	0.86 (0.75;0.98)	0.95 (0.78;1.16)	0.80 (0.67;0.95)
Smoking			
Former	1.12 (0.84;1.49)	1.66 (1.01;2.73)	0.92 (0.65;1.31)
Current	1.49 (1.06;2.09)	2.45 (1.41;4.24)	1.12 (0.73;1.73)
Stroke	2.50 (1.48;4.23)	2.91 (1.40;6.06)	2.22 (1.14;4.33)

Values represent odds ratios and 95% confidence intervals, adjusted for all other risk factors and additionally for time between measurements and MCI diagnosis. *Abbreviations: MCI=mild cognitive impairment, CI=confidence interval, n=number of cases, N=number of controls, APOE=apolipoprotein E, SD=standard deviation, HDL=high-density lipoprotein.*

Table 4. Association between MCI and MRI markers of brain pathology (cross-sectional).

	Volumetric measures Mean difference (95% CI)			Microstructural integrity measures Mean difference (95% CI)		Focal measures Odds ratio (95% CI)	
Model I	**Total brain**	**Hippocampus**	**WML**	**FA**	**MD**	**Microbleeds**	**Lacunes**
No MCI	Reference	Reference	Reference	Reference	Reference	Reference	Reference
MCI	-6.66 (-15.61;2.28)	0.01 (-0.07;0.08)	0.34 (0.11;0.58)	-0.003 (-0.008;0.001)	0.007 (-0.001;0.016)	1.42 (0.73-2.75)	2.68 (1.11-6.45)
Amnestic	-8.37 (-21.16;4.42)	0.05 (-0.06;0.15)	0.32 (-0.02;0.65)	-0.001 (-0.007;0.006)	0.003 (-0.009;0.016)	1.55 (0.61-3.95)	2.31 (0.69-7.68)
Non-amnestic	-5.04 (-17.10;7.01)	-0.03 (-0.13;0.07)	0.36 (0.05;0.68)	-0.006 (-0.012;0.001)	0.010 (-0.001;0.022)	1.35 (0.55-3.31)	3.16 (0.98-10.19)
Model II	**Total brain**	**Hippocampus**	**WML**	**FA**	**MD**	**Microbleeds**	**Lacunes**
No MCI	Reference	Reference	Reference	Reference	Reference	Reference	Reference
MCI	-6.37 (-15.31;2.57)	-0.01 (-0.08;0.07)	**0.35 (0.11;0.58)**	**-0.004 (-0.009;0.001)**	**0.007 (-0.001;0.016)**	**1.51 (0.77-2.98)**	**2.55 (0.99-6.54)**
Amnestic	-6.78 (-19.57;6.01)	0.04 (-0.07;0.15)	0.21 (-0.13;0.55)	-0.000 (-0.007;0.007)	0.001 (-0.012;0.013)	1.51 (0.58-3.97)	1.77 (0.49-6.36)
Non-amnestic	-5.77 (-17.86;6.32)	-0.03 (-0.13;0.07)	0.46 (0.14;0.78)	-0.007 (-0.014;-0.001)	0.013 (0.001;0.024)	1.55 (0.62-3.89)	3.83 (1.08 13.61)

Model I: adjusted for age and sex.

Model II: adjusted for age, sex, *apolipoprotein E*-ε4 carriership, waist circumference, hypertension, diabetes mellitus, total and high-density lipoprotein cholesterol, and smoking. Model II was a complete case analysis Analyses involving volumetric or microstructural integrity measures were additionally adjusted for intracranial volume.

Volumetric measures were expressed in milliliter (ml), FA has no unit, and MD is expressed in 10^{-3} mm^2/sec. Focal measures were expressed as present versus absent.

Abbreviations: MCI= mild cognitive impairment, MRI=magnetic resonance imaging, CI=confidence interval, WML= white matter lesions volume, FA= fractional anisotropy, MD= mean diffusivity.

Table 5. Associations between MCI and risk of dementia, Alzheimer's disease, and mortality (longitudinal)

	Dementia		Alzheimer's disease		Mortality	
	n/N	Hazard ratio (95% CI)	n/N	Hazard ratio (95% CI)	n/N	Hazard ratio (95% CI)
Model I						
No MCI	149/3,781	Reference	122/3,781	Reference	695/3,781	Reference
MCI	66/417	3.98 (2.97;5.33)	55/417	4.03 (2.92;5.56)	132/417	1.54 (1.28;1.85)
Amnestic MCI	35/163	6.89 (4.74;10.01)	29/163	7.21 (4.77;10.89)	50/163	1.74 (1.30;2.31)
Non-amnestic MCI	31/254	2.65 (1.79;3.92)	26/254	2.69 (1.75;4.12)	82/254	1.44 (1.14;1.81)
Model II						
No MCI	140/3,541	Reference	114/3,541	Reference	653/3,541	Reference
MCI	59/389	3.70 (2.70;5.05)	49/389	3.75 (2.66;5.30)	123/389	1.48 (1.22;1.80)
Amnestic MCI	33/154	6.76 (4.55;10.03)	27/154	7.20 (4.64;11.18)	46/154	1.58 (1.17;2.14)
Non-amnestic MCI	26/235	2.30 (1.50;3.54)	22/235	2.38 (1.49;3.80)	77/235	1.41 (1.12;1.80)

Model I: adjusted for age and sex. Model II: adjusted for age, sex, *apolipoprotein E*-ε4 carriership, waist circumference, hypertension, diabetes mellitus, total and high-density lipoprotein cholesterol, smoking, stroke, and educational level. Values represent hazard ratios and 95% confidence intervals.
Abbreviations: n=number of cases, N=number of persons at risk, CI=confidence interval, MCI=mild cognitive impairment.

DISCUSSION

We found that in the general population, older age, *APOE*-ε4 carriership, lower total cholesterol levels, and prevalent stroke were associated with MCI. Lower HDL-cholesterol levels and current smoking were only related to MCI when assessed up to 7 years prior to MCI screening. Compared to cognitively healthy participants, participants with MCI had larger WML volumes, worse microstructural integrity of normal-appearing white matter, and a higher frequency of lacunes. MCI was associated with an increased risk of dementia, Alzheimer's disease, and mortality.

Major strengths of our study are its population-based setting, large sample size, and extensive data collection. Some limitations of our study need to be considered. Firstly, the extensive neuropsychological test battery required for the MCI diagnosis was implemented in 2002-2005 (baseline), and therefore we were not able to assess MCI status on the examination rounds prior to baseline. Therefore, it is possible that some persons may already have had MCI at the previous examination round. Secondly, the cross-sectional setting in the analyses of risk factors prevented inferring causality. However, the extensive data collection enabled us to investigate determinants both cross-sectionally at baseline and 7 years prior to baseline, overcoming reverse causality in our study. Thirdly, we did not measure visuospatial ability, and could therefore not include this component in our diagnostic criteria for MCI. Finally, MRI scanning was performed on average 1.01 years (SD 0.46) later than the initial screening for

MCI, and misclassification of participants may be present. Nonetheless, 90% of our study participants underwent MRI within 1.5 years of MCI screening, and if present this non-differential misclassification would have led to an underestimation of the true association. Also, we repeated the analyses after excluding incident dementia cases, and found that results did not change materially. We found that some determinants of MCI differed over time. Lower HDL-cholesterol levels and current smoking were only related to MCI when assessed up to 7 years prior to MCI screening. There is a possibility that persons with a declining cognitive ability change their daily habits, including dietary and smoking habits, which could result in reverse causality in cross-sectional analysis. Another explanation is that these associations indeed differ over time, as has been shown for several risk factors for dementia.[4, 40]

In line with previous clinical and population-based studies, we found that people with MCI had larger WML volumes, worse microstructural integrity of normal-appearing white matter, and a higher prevalence of lacunes compared to cognitively healthy participants.[23, 41-43] As regional measurements of DTI were not available in our study, we examined DTI measures averaged over the entire normal appearing white matter. For future investigations however, it would be interesting to study regional differences in FA and MD. MCI was not associated with total brain volume, hippocampal volume, and cerebral microbleeds. These imaging markers have been implicated in persons with MCI before,[44-49] but relatively small sample size hampered our ability to investigate these associations more thoroughly. Also, smaller total brain volume, hippocampal volume and microbleeds may mark more downstream neuropathology and as such would be a better marker for clinical dementia rather than the transitional stage of MCI.[50]

Participants with MCI had an increased risk of dementia and an increased risk of mortality, independently of several risk factors of dementia. Because of this poorer prognosis, our findings underline the importance of identifying persons with MCI.

It is hypothesized that different subtypes of dementia are preceded by different subtypes of MCI. Amnestic MCI is supposed to especially increase the risk of Alzheimer's disease, whereas non-amnestic MCI more likely increases the risk of vascular dementia and other dementia subtypes, such as Lewy body dementia and frontotemporal dementia.[51, 52] This would suggest that determinants might also differ per subtype of MCI. However, our findings propose that this distinction is not as unambiguous. On the one hand, we found that there are indeed some differences in determinants for amnestic and non-amnestic subtypes; e.g. *APOE*-ε4 carriership and smoking were related to amnestic MCI only and MRI-correlates of vascular damage, such as larger WML load, altered diffusion tensor imaging measures, and lacunes, were more strongly related to non-amnestic MCI. On the other hand, we found that persons with MCI who converted to dementia, most often converted to Alzheimer's disease, regardless of

the MCI subtype. Moreover, stroke was related to both subtypes of MCI. Our results therefore suggest that accumulating vascular damage plays a role in both amnestic and non-amnestic MCI. This is consistent with the fact that vascular disease not only plays an important role in vascular dementia, but also in Alzheimer's disease.[2-4, 17, 53, 54] Therefore, we propose that timely targeting modifiable vascular risk factors might contribute to the prevention of MCI and dementia. Nonetheless, it should be kept in mind that the cross-sectional setting of our study in the analyses of risk factors prevents us from drawing any conclusions regarding causality.

We found that persons with amnestic MCI had a larger risk of dementia than persons with non-amnestic MCI. This difference might be a consequence of the definitions of the MCI subtypes. Study participants with amnestic MCI may have experienced difficulties on other cognitive domains besides memory alone, while participants with non-amnestic MCI per definition did not experience any memory problems. Hence, persons with amnestic MCI may have been cognitively more impaired than persons with non-amnestic MCI.

In conclusion, in our population-based study we found that several vascular risk factors and MRI-correlates of cerebrovascular disease were associated with MCI. Persons with MCI had an increased risk of dementia, Alzheimer's disease, and mortality.

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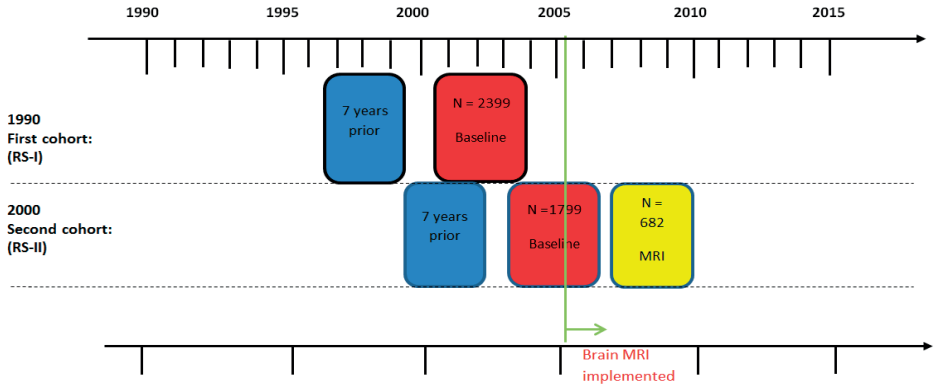
Supplementary Table 1. Characteristics of the included and excluded participants

	Examinations at baseline 2002-2005		Examinations before baseline 1997-2001	
	Included in analysis N=3,930	**Excluded from analysis N=268**	**Included in analysis N=3,583**	**Excluded from analysis N=615**
Age, years	71.8 (7.2)	71.2 (7.2)	67.5 (7.0)	67.3 (7.0)
Females	57.0%	66.0% [a]	56.3%	64.4% [a]
APOE-ε4 carrier	26.5%	26.3%	26.9%	23.9%
Waist circumference, cm	93.5 (11.8)	94.5 (12.8)[a]	93.0 (12.3)	93.1 (11.5)
Hypertension	80.4%	86.9% [a]	64.9%	72.1% [a]
Diabetes mellitus	14.4%	17.9%	8.6%	7.5%
Cholesterol, mmol/l	5.62 (0.99)	5.79 (1.03)	5.84 (0.96)	5.76 (1.00) [a]
HDL-cholesterol, mmol/l	1.45 (0.40)	1.45 (0.40)	1.40 (0.39)	1.33 (0.36)
Smoking				
Former	55.5%	50.0%	51.2%	44.8%
Current	15.2%	18.3%	19.0%	22.7%
Stroke	3.9%	3.0%	2.3%	1.6%

[a] Significantly different ($p<0.05$) between included participants and excluded participants, after sex and age adjustment – if applicable. Participants excluded from the analysis missed at least one value of the determinants mentioned in the table.



Supplementary Figure 1. Assessment of determinants, MCI and MRI examination
In red: baseline measurement of determinants and MCI assessed in 2002-2005. In blue: measurement of determinants assessed in the examination round 7 years prior to baseline. In yellow: a random subset of 682 persons with MCI screening at baseline and brain MRI examination performed on average 1.01 years after baseline (2005 onwards). Abbreviations: MCI= mild cognitive impairment, MRI=magnetic resonance imaging, RS = Rotterdam Study.