# Supplementary Table 5. Characteristics of ADNI studies

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| **Arbizu 2013** | |
| **Patient sampling** | Study design: nested case-control study; retrospective analysis of longitudinal data from ADNI database  Participants with baseline 18F-FDG PET scan were recruited from ADNI database: 80 healthy subjects (HS), 36 patients with mild cognitive impairment (MCI) who converted to AD dementia within 18 months, 85 non-converter MCI patients who did not convert within 24 months, and 67 with AD dementia. Additionally, participants were recruited from patients at Clínica Universidad de Navarra for model validation: 20HS (vHS), 27 MCI patients (vMCI; six of whom converted within the 18-month follow-up, vMCI-C) and 21 AD patients (vAD). We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable.  Exclusion criteria: not reported |
| **Patient characteristics and settings** | 121 participants diagnosed by Petersen 2004 criteria: 36 MCI-AD and 85 MCI-MCI  Gender: women 15 and men 21 MCI converters; women 25 and men 60 non-MCI converters  Age(y): MCI converters 77 (range 65-89); non-MCI converters 77 (range 65-87)  APOE ε4 carrier: MCI converters 24/36 (67%); non-MCI converters 37/85 (43%)  MMSE: MCI converters 27 (range 24-29); non-MCI converters 28 (range 24-30)  Education (y): MCI converters 16 (range 12-20); non-MCI converters 16 (range 7-20)  Sources of referral: not reported  Setting: multicenter |
| **Index test** | 18F-FDG PET scan  *Acquisition*  Static emission images of 20-min duration were acquired 40 min after injection of 5.3 MBq/kg of 18F-FDG  *Data analysis*  Images were processed using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm).  Threshold: AD conversion score: the optimal cut-off=0.28; not pre-specified  Note: AD-conversion score is a combination of hypo-metabolism in the posterior cingulate area together with the APOE4 genotype and MMSE score (age and gender) |
| **Target condition** | Target condition: conversion from MCI to Alzheimer’s disease dementia  Reference standard: NINCDS-ADRDA |
| **Flow and timing** | Duration of follow-up: 24 months  Number included in analysis (N=121)  At follow-up: 36 MCI-AD (disease positive); 85 MCI-MCI (disease negative) (Table 1, p1397)  Conversion from MCI to ADD  Sensitivity=92%%; specificity=62% (p1399-p1400) for AD score (18F-FDG PET data & Age & Gender)  TP=33; FP=32; FN=3; TN=53; PPV=51%; NPV=95% (Calculated in Revman5). |
| **Notes**  The authors contacted in order to obtain the data for creating 2X2 table for 18F-FDG PET scan *alone*. They only reported the values for the AUC.  Dr Arbizu Email (12/3/16): *“The AUC for hypometabolism in all cortical regions was 0.739 (95 % CI 0.641 – 0.838). However, according to the univariable and multivariable models performed to select the best discriminant cortical regions within the AD pattern, only hypometabolism in the posterior cingulate area was significant in the multivariable model (Table 2). Moreover, among the clinical variables evaluated, ApoE4 genotype and MMSE score had a significant effect in both the univariable and multivariable models, while education level did not show a significant independent effect (Table 2). When the MMSE score and ApoE4 genotype (age and gender) were considered in the model, the AUC was 0.742**(95 % CI 0.646 – 0.838). However, when posterior cingulate hypometabolism was also included in the model, the AUC improved significantly to 0.804 (95 % CI 0.714 – 0.894, bootstrap p=0.027)”.*  **Objective:** to evaluate the accuracy of multimodal probabilistic prediction of conversion to AD dementia in patients with MCI  **Conclusion**  “Posterior cingulate metabolism, when compared in a multivariable model with age and gender as well as MMSE score and ApoE4 data, improved the determination of the likelihood of patients with MCI converting to AD dementia compared with clinical variables alone”. | |
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| **Dukart 2016** | |
| **Patient sampling** | Study design: nested-case control study; retrospective analysis of longitudinal data from ADNI database  ADNI participants recruited; Training data: 144 AD and 122 healthy controls; Testing data: 177 MCI-converters and 265 MCI-stable. Sampling process not described.  We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable.  Exclusion criteria: not reported |
| **Patient characteristics and settings** | 164 MCI participants: 29 MCI-converters and 135 MCI-stable (Table 1, p1145). MCI diagnostic criteria not reported.  Gender: MCI converters: 11 women, 18 men; MCI non-converters: 51 women, 84 men  Age (y): MCI converters 73±8.1 (range 55-85); MCI non-converters 73±7.5 (range 48-88)  APOE ε4 carrier: not reported  MMSE: MCI converters 27±1.7; MCI non-converters 28.1±1.6  Education (y): MCI converters 16.3±2.6 (range 9-20); MCI non-converters 15.7±2.8 (range 8-20)  Sources of referral: not reported  Setting: multicenter  Note  MCI diagnostic criteria in ADNI studies (http://adni.loni.usc.edu/study-design/background-rationale/)  *“MCI participants have reported a subjective memory concern either autonomously or via an informant or clinician. However, there are no significant levels of impairment in other cognitive domains, essentially preserved activities of daily living and there are no signs of dementia. Levels of MCI (early or late) are determined using the Wechsler Memory Scale Logical Memory II”* |
| **Index test** | 18F-FDG PET scan  *Acquisition*  Not described. FDG PET data were downloaded at the most advanced pre-processing stage provided by ADNI.  *Data analysis*  Pre-processing of all images data was performed in SPM8. Naıve Bayes (NB) classification algorithm was used to evaluate the predictive accuracy of different genetic, neuropsychological, and imaging biomarkers for differentiation between cMCI and sMCI. NB classifiers were first built using all available AD and HC data separately for each of the modalities. The obtained NB classifiers were then applied to MCI data having the same biomarker constellations.  An assignment of sMCI as HC and of cMCI as AD was considered as correct. Balanced accuracies ((sensitivity+specificity)/2), sensitivities, specificities, receiver operating characteristics (ROC) curves, and the area under the curve (AUC) were computed based on predicted labels by each NB output.  Threshold: no single threshold value report possible for FDG-PET as the decision was made by the classifier based on the pattern seen in a set of AD relevant regions (s. supplement .nii images) (Dr, Dukart’ email on 16/3/2016) |
| **Target condition** | Target condition: conversion from MCI to Alzheimer’s disease dementia  Reference standard: NINCDS-ADRDA |
| **Flow and timing** | Duration of follow-up: average for sMCI= 27 month; average for cMCI=36 month  Number included in analysis (N=164)  Conversion to AD  At follow-up: 29 MCI-converters (disease positive); 135 MCI-non-converters (disease negative)  Sensitivity=90%; specificity=84% (Table 2, p1150)  TP=26; FP=22; FN=3; TN=113 (Calculated in Revman5) |
| **Notes**  The author contacted and confirmed (Dr. Dukart’s email on 16/3/2016) that the sensitivity and specificity values for 18F-FDG PET scan alone in Table 2 correspond to 135 sMCI and 29 pMCI (Table 1); additional missing data provided.  **Objective:** to evaluate the most promising combinations of a variety of imaging, neuropsychological and genetic biomarkers for the accurate prediction of conversion to AD.  **Hypothesis:** a combination of biomarkers covering several genetic, behavioral, and neuropathological factors will provide higher sensitivity for early AD detection and disease staging as compared to best performing single modality biomarker.  **Conclusion**  “As a single marker, 18F-FDG PET scan had the highest accuracy (76%)… When including further imaging modalities and genetic information, this accuracy increased to about 87%. Fully independent classifiers, built only on AD and controls data, and combining imaging, genetic, and/or neuropsychological biomarkers can more reliably discriminate between stable and converter MCI than single modality classifier”. | |
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| **Gomar 2011** | |
| **Patient sampling** | Study design: nested case-control study; retrospective analysis of longitudinal data from ADNI database  MCI participants with a number of baseline cognitive tests and biomarkers (18F-FDG PET scan, MRI and CSF measures) were recruited from ADNI database. We only included data on performance of 18F-FDG PET scan alone to discriminate between patients with MCI who convert to dementia and those who remained stable.  Exclusion criteria: MCI subjects whose conversion to AD was not verified at another additional follow-up (i.e., at least two consecutive visits being diagnosed as AD and no reversion to MCI). |
| **Patient characteristics and settings** | 162 MCI participants diagnosed with the Petersen 2010 criteria who had 18F-FDG PET scan at baseline. At follow-up: 74 MCI-converters and 88 MCI-non-converters (Table 3, p708). Demographic characteristics are reported for 318 MCI participants: 150 MCI-converters and 168 MCI-non-converters (Table 1, p707).  Gender: MCI converters: 60 women, 90 men; MCI non-converters: 59 women, 109 men  Age (y): MCI converters 74.92±7.03; MCI non-converters 75.02±7.51  APOE ε4 carrier: MCI converters 96/150 (64%); MCI non-converters 70/168 42%)  MMSE: MCI converters 15.63±12.91; MCI non-converters 15.77±3.11  Education (y): MCI converters 16.3±2.6 (range 9-20) ; MCI non-converters 15.7±2.8 (range 8-20)  Sources of referral: not reported  Setting: multicenter |
| **Index test** | 18F-FDG PET scan  Acquisition  Not described. 18F-FDG PET scan data are provided by ADNI.  Data analysis  A voxel wise approach; the HCI was used. This is a single measure intended to reflect the extent to which the pattern and magnitude of cerebral hypometabolism in an individual correspond to that in probable AD patients. A specified reconstruction algorithm for each scanner type was implemented according to a standardized protocol to acquire FDG-PET data (http://www.loni.ucla.edu/ADNI/Data/ADNI\_Data.shtml). All images were pre-processed by the ADNI positron emission tomography (PET) coordinating center. The processing involved a voxel wise approach to analyze the data using statistical parametric mapping (SPM) performed by the Banner Alzheimer’s Institute.  Threshold: not reported |
| **Target condition** | Target condition: conversion from MCI to Alzheimer’s disease dementia  Reference standard: not reported |
| **Flow and timing** | Duration of follow-up: 4 years (mean follow-up time 33.28 months; range 7.26–61.44; mean time until conversion 20.44 months; range 5.75–52.63).  Number included in analysis (**N=162**)  Conversion to AD  At follow-up: 74 MCI-AD (disease positive); 88 MCI-MCI (disease negative) (table 3, p708)  AUC=0.70 (Table 4, p709)  Sensitivity=47**%**; specificity=73%at 0.50 probability level for 18F-FDG PET alone using the HCI.  TP=35; FP=24; FN=39; TN=64 (Calculated in RevMan5) |
| **Notes**  The author contacted and provided a ‘Classification Table’ (Dr. Gomar’s email on 30/3/2016), which shows a range of ‘sensitivity’ and ‘specificity’ values at different probability levels’  **Objective:** to examine the predictive value of different markers in the progression from MCI to AD over 4-year follow-up, and to derive and validate a model for prediction.  **Conclusion**  “Cognitive markers were more robust predictors than biomarkers. The study highlights the importance of cognitive measures in progression from MCI to AD at 4 years of follow-up as they were found to be at 2 years of follow-up… The HCI index of 18F-FDG PET at baseline was also predictive of conversion to MCI in a univariate model”. | |
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| **Herholz 2011** | |
| **Patient sampling** | Study design: retrospective analysis of longitudinal data from ADNI database  A subset of 94 MCI participants' baseline data, available for all measures of interest, was used from the ADNI, a multicenter project with approximately 50 medical center and university sites across the United States and Canada.  Exclusion criteria: not reported. |
| **Patient characteristics and settings** | 94 participants with MCI, diagnosed with the Petersen 2010 and CDR = 0.5 at baseline, were recruited from ADNI data.  Gender: 28 women, 66 men  Age (y): Total: 75.0 ± 7.6 years  APOE ɛ4: not reported  MMSE: 27.1 ± 1.59  Education (y): not reported  Sources of referral: not reported  Sources of recruitment: multicenter |
| **Index test** | ¹⁸F-FDG PET scan  *Acquisition*  PET scans represented the brain activity 30–60 min after injection of 18F-FDG; had been reconstructed using 3-dimensional back projection, 3-dimensional ordered-subset expectation maximization, or Fourier rebinning/2-dimensional ordered-subset expectation maximization; were scaled to a common global average value; and were reoriented into a standard 160X160X96 voxel image grid (voxel size, 1.5x1.5x1.5 mm) along the anterior commissure-posterior commissure (AC-PC) plane and formatted as DICOM or ECAT files.  *Data analysis*  The AD t-sum was calculated. It indicates the severity of the metabolic decrease in those brain areas that are typically affected by AD (multimodal association cortices mostly located in the temporal and parietal lobes), including an adjustment for age effects. The AD t-sum was converted into a PET score by reference to its upper limit (Herholz 2002)  ROI: temporal and parietal lobes  PET score = log2 {(ADtsum/11,089) + 1)}  Threshold: rCGMglc of t sum > 11.090 (Herholz 2002); pre-specified. |
| **Target condition** | Target condition: conversion from MCI to Alzheimer's disease dementia  Reference standard: clinical dementia rating (not specified) and ADAS-cog  Unclear whether clinicians conducting follow-up were aware of the ¹⁸F-FDG results |
| **Flow and timing** | Duration of follow-up: 24 months  Participants were required to have had four ¹⁸F-FDG PET scans at baseline, 6m, 12m, and 24m.  At 24-month follow-up: 30 MCI-ADD, 64 MCI-non-convertors (57 MCI-MCI; 7 MCI-normal cognition); 45% abnormal ¹⁸F-FDG tests (Table 2, p 1220): 38 test positive; 56 test negative  Number included in analysis: 94  Sensitivity=57%; specificity=67% (p 1220)  TP = 17; FP = 21; FN = 13; TN = 43 (Calculated in Review Manager 5)  Loss to follow-up: none |
| **Objective:** to evaluate a calibrated 18F-FDG PET score as a biomarker for progression in AD and MCI  **Conclusion**  “18F-FDG PET scores at study entry in MCI patients significantly predict clinical progression to dementia with higher accuracy than MMSE and ADAS-cog. As a measure of disease progression, PET score may provide a power for 1-years study in MCI patients similar to what they provide for 2-years studies based on progression of ADAS-cog score”. | |
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| **Landau 2010** | |
| **Patient sampling** | Study design: retrospective analysis of longitudinal data from ADNI database  Participants with MCI were recruited from the ADNI, a multicenter project with approximately 50 medical center and university sites across the United States and Canada. Participants had MCI and baseline data were available for all measures of interest to the current study.  Exclusion criteria: not reported |
| **Patient characteristics and settings** | 85 participants with MCI diagnosed with Petersen 2010 and CDR=0.5 criteria. MCI participants were classified as single-domain or multi-domain amnestic MCI (Petersen 2003).  Gender: 56 men; 29 women. MCI-non-converters: 37M, 20F; MCI-converters: 19M, 9F  Age (y): MCI-non-converters: mean 78 ± 7.4 years; MCI-converters: mean 78.3 ± 7.5  APOE ɛ4: MCI-non-converters: 14 (25%); MCI-converters: 11 (41%)  MMSE: MCI-non-converters: mean 27.3 ± 1.6; MCI-converters: mean 26.4 ± 1.7  Education (y): MCI-non-converters: mean 16.3 ± 2.8; MCI-converters: mean 16.4 ± 2.6  Sources of referral: not reported  Sources of recruitment: multicenter |
| **Index test** | ¹⁸F-FDG PET scan  *Acquisition*  PET images were acquired 30–60 minutes post-injection. Images were averaged, spatially aligned, interpolated to a standard voxel size, intensity normalized, and smoothed to a common resolution of 8 mm full width at half maximum.  *Data analysis*  Spatial normalization of each individual’s PET volume to the standard ¹⁵O-H₂O PET template was conducted using **SPM5** (template voxel dimensions: 91 x 109 x 91; voxel size: 2 mm x 2 mm x 2 mm).  The regions of interest (ROI) selected were study-independent, frequently associated with decline in AD and MCI (no further details). Optimal diagnostic thresholds were derived from a ROC analysis.  Threshold: 1.21 (Table 2 – most likely this value refers to rCMRglc); not pre-specified.  The mean ± SD values on ¹⁸F-FDG scan are referred on Table 1: MCI-non-converters: 1.22 ± 0.14; MCI-converters: 1.13 ± 0.10 |
| **Target condition** | Target condition: conversion from MCI to Alzheimer's disease dementia  Reference standard: NINCDS-ADRDA criteria. Cognitive decline was measured by ADAS–Cognitive Subscale (Rosen 1984) and standard diagnostic criteria.  Unclear whether clinicians conducting follow-up were aware of the ¹⁸F-FDG PET results. |
| **Flow and timin**g | Duration of follow-up: Mean = 1.9 ± 0.4 years; On average: 2 years  Follow-up occurred at multiple time points (6, 12, 18, 24 and 36 months)  At baseline 85 participants with MCI.  At follow-up: 85 participants: 28 MCI-ADD; 57 MCI-MCI (p 232)  Information from the author:  At follow-up: 51 MCI with positive ¹⁸F-FDG biomarker: 21 MCI-ADD, 30 MCI-MCI; 34 MCI with negative ¹⁸F-FDG biomarker: 7 MCI-ADD, 27 MCI-MCI  Number included in analysis: 85  TP = 21; FP = 30; FN = 7; TN = 27 (Dr Landau’s email on 24/1/2013).  Sensitivity 75%; specificity=47% (Calculated in RevMan5)  Loss to follow-up: none; all 85 participants appear to be included in the analysis. |
| **Notes**  We contacted the trial investigators who provided relevant data for the 2 x 2 table to be completed (Dr Landau’s email on 24/1/2013).  **Objective:** to evaluate the prognostic ability of genetic, CSF, neuroimaging, and cognitive measurements obtained in the same participants; to compare predictors of conversion and decline in participants with MCI  **Conclusion**  “In the multivariate model only baseline ¹⁸F-FDG PET and episodic memory predict conversion from MCI to AD, whereas CSF p-tau181p/ ABeta1-42 and, marginally ¹⁸F-FDG PET alone predict longitudinal cognitive decline.” | |
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| **Lange 2016** | |
| **Patient sampling** | Study design: nested case-control study; retrospective analysis of longitudinal data from ADNI database  Participants with MCI, AD participants and healthy controls were recruited from the ADNI.  We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable.  Exclusion criteria: conversion to non-AD dementia |
| **Patient characteristics and settings** | Diagnostic criteria for MCI not reported.  Original sample: 108 MCI: 31 MCI-AD and 77 MCI-MCI (downloaded from the ADNI database in March 2014)  Gender: MCI-converters: 12 women, 19 men; MCI-non-converters: 23 women, 54 men  Age (y): MCI converters 74.7±6.4 years; MCI-non-converters 74.5± 7.7years  APOE ε4 carrier: not reported  MMSE: MCI converters 27.1±1.4; MCI-non-converters 27.7±1.6  Education (y): MCI converters 15.8±3.0 years; non-MCI converters 16.0±2.7 years  Sources of referral: not reported  Setting: multicenter  Validation sample: 241 MCI: 60 MCI-AD and 181MCI-MCI (downloaded from the ADNI database in August 2015)  Gender: MCI-converters: 23 women, 37 men; MCI-non-converters: 86 women, 95 men  Age (y): MCI converters 73.7±6.5 years; MCI-non-converters 70.5±7.2 years  APOE ε4 carrier: not reported  MMSE: MCI converters 27.2±1.7; MCI-non-converters 28.2±1.6  Education (y): MCI converters 16.2±2.7 years; non-MCI converters 16.3±2.6 years  Sources of referral: not reported  Setting: multicenter |
| **Index test** | [18F]FDG PET scan  *Acquisition*  In 152 out of the total of 172 subjects, FDG PET had been acquired according to a dynamic protocol so that 6 frames of 5 min duration from 30 to 60 min post injection were available for analysis. The remaining 20 FDG PETs had been acquired as 30 min static emission scan starting 30 min post injection.  *Data analysis*  The Herzholz t-sum score approach was used. However, the PALZ tool in PMOD software was not used but rather the Herholz method was implemented in a MATLAB/SPM processing pipeline. The AD-meta-ROI was created over which the t-values of the voxel-based test are summed. This AD-meta-ROI is similar to but not exactly equal to the AD-meta-ROI implemented in PMOD. Therefore, the threshold of 11090 usually used with the PALZ tool was not applicable in our analyses. The t-sum score is computed from the statistical parametric map (SPM) of the one-sided t-test of the individual patient’s FDG PET versus a database of FDG-PETs of healthy normal subjects. Thus, computation of the t-sum score requires ‘single case-SPM. Visual reading was not perform (Dr. Buchert’s email on 13/5/2016)  Threshold: not pre-specified; *ROC-analysis* was used to determine the optimal cut-off (Youden criterion) and 100 repeats of 20-fold cross-validation to avoid overly optimistic accuracy estimates.  t-sum score  Original sample: MCI converters: 37817±20182; MCI-non-converters: 14400±17483  Validation sample: MCI converters: 28356±20085; MCI-non-converters: 14604±16754 |
| **Target condition** | Target condition: conversion from MCI to Alzheimer’s disease dementia  Reference standard: not reported |
| **Flow and timing** | Conversion from MCI to ADD; duration of follow-up: 3 years  *Original sample*  Number included in analysis (N=108)  At follow-up: 31 MCI-AD (disease positive); 77 MCI-MCI (disease negative)  **AUC=0.728** with the SPM default setting  **AUC=0.832** with the SPM ‘optimized’ setting  *Validation sample*  Number included in analysis (**N=241**)  At follow-up: 60 MCI-AD (disease positive); 181 MCI-MCI (disease negative)  Sensitivity=58%; specificity=56%; PPV=31%; NPV=80%; **AUC=0.675** with the SPM default setting  Sensitivity=70%; specificity=68%; PPV=42%; NPV=87%; **AUC=0.746** with the SPM ‘optimized’ setting |
| **Notes**  Additional information were requested and obtained from the trial investigators regarding metrics used (Dr Buchert’s email on 30/5/2016).  **Aim:** to optimize the processing pipeline of voxel-based single subject analysis for prediction of MCI to AD conversion by brain FDG PET within the framework of SPM.  The following aspects of the processing pipeline were considered: frame-by-frame motion correction, [O-15]-water versus FDG template, spatial smoothing, and intensity scaling. Optimizing SPM for voxel-based single subject analysis of brain 18F-FDG PET provided considerable improvement of MCI to AD prediction.  **Conclusion**  “The prognostic value of voxel-based single subject analysis of brain 18F-FDG PET in MCI subjects can be improved considerably by optimizing the processing pipeline”. | |
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| **Prestia 2013** | |
| **Patient sampling** | Study design: nested cross-sectional study; retrospective analysis of longitudinal data from ADNI database  Participants were retrospectively and independently recruited from ADNI and TOMC (Translational Outpatient Memory Clinic). Sampling procedure not described. We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable.  Exclusion criteria: cognitive disturbance accountable by focal cerebral, physical, psychiatric, or metabolic diseases |
| **Patient characteristics and settings** | 93 participants diagnosed by Petersen 199 criteria: ADNI cohort: 24 MCI with pAD (prodromal AD) and 33 sMCI (stable);  TOMC cohort: 18 MCI with pAD and 18 sMCI  Gender: ADNI: MCI converters 10 women and 14 men; MCI non-MCI converters 13 women and 20 men; TOMC: MCI converters 12 women and 6 men; non-MCI converters 9 women and 9 women  Age (y): ADNI MCI converters 75±8 (range 55-89); non-MCI converters 75±8 (range 55-89); TOMC: MCI converters 71±8 (range 54-83); non-MCI converters 72.8±(range 51-85)  APOE ε4 carrier: not reported  MMSE: ADNI: MCI converters 28±2 (range 24-29; non-MCI converters 27±2 (range 24-30)  Education (y): not reported  Sources of referral: not reported for ADNI patients; TOMC patients are self-referred or referred by general practitioners or specialists  Setting: multicenter |
| **Index test** | 18F-FDG PET scan  Acquisition  ADNI FDG-PET images were acquired using 17 different scanner models from three vendors (Philips, Siemens, and General Electric) with varying manufacturers’ countries. PET sites were approved initially for PET scanning by performing a pair of phantom scans on the three-dimensional Hoffman brain phantom following a protocol that matched the acquisition and reconstruction parameters to be used for the human phase of the ADNI project.  Data analysis  FDG-PET indices of AD-related hypometabolism were the PMOD Alzheimer’s discrimination analysis tool (PALZ), the hypometabolic convergence index (HCI), and the meta-region of interest (ROI) average. All metrics are based on voxel-by-voxel analysis of 18F-FDG PET scans and provide a single measure of AD-related hypometabolism; however, they are computed using different processing procedures.  Thresholds: cut-offs were computed based on their performance in correctly identifying 148 elderly with normal cognition (normative dataset), imposing 95% level of specificity.  PALZ (sum of t-scores within a predefined AD mask) t=13,48 for ADNI; t=13,481 for TOMC  HCI (inner-product of individual and pre-defined AD Z-score maps): 1.055 for both ADNI and TOMC  Meta ROI average (average of mean counts in 5 meta ROI volumes): w=2.60 for both ADNI and TOMC |
| **Target condition** | Target condition: conversion from MCI to Alzheimer’s disease dementia  Reference standard: NINCDS-ADRDA |
| **Flow and timing** | Duration of follow-up: mean 26±12 months (range 12-36 months) TOMC cohort; mean 36±12 months (range 12-48 months) ADNI cohort.  Conversion from MCI to ADD  **ADNI cohort** (Table 3, p17)  Number included in analysis (N=57)  At follow-up: 24 MCI-AD (disease positive); 33 MCI-MCI (disease negative)  PALZ: sensitivity=33%; specificity=67%  TP=8; FP=11; FN=16; TN=22; PPV=42%; NPV=58% (Calculated in Revman5)  HCI: sensitivity=63%; specificity=61%  TP=15; FP=13; FN=9; TN=20; PPV=54%; NPV=69% (Calculated in Revman5)  MetaROI: sensitivity=46%; specificity=58%  TP=11; FP=14; FN=13; TN=19; PPV=44%; NPV=60% (Calculated in Revman5)  **TOMC cohort** (Table 3, p17)  Number included in analysis (N=36)  At follow-up:18 MCI-AD (disease positive); 18 MCI-MCI (disease negative)  PALZ: sensitivity=78%; specificity=72%  TP=14; FP=5; FN=4; TN=13; PPV=73%; NPV=77% (Calculated in Revman5)  HCI: sensitivity=72%; specificity=56%  TP=13; FP=8; FN=5; TN=10; PPV=61%; NPV=66% (Calculated in Revman5)  MetaROI: sensitivity=56%; specificity=83%  TP=10; FP=3; FN=8; TN=15; PPV=77%; NPV=65% (Calculated in Revman5) |
| **Notes**  The authors contacted and confirmed that the same patients were included in both papers, Prestia 2013 and Prestia 2015a.  For this systematic review we only considered the accuracy of 18F-FDG PET biomarkers for progression from MCI to AD dementia.  **Results**  The preliminary findings provide further evidence to the revised NIA-AA criteria for AD and suggest that Abeta42 concentrations and hippocampal volumes may be used in combination to best identify prodromal AD.  Despite variable between datasets, the three metrics of hypometabolism showed intermediate sensitivity and specificity patterns. These results are in line with recent studies finding that parietotemporal and posterior cingulate hypometabolism on 18F-FDG PET is less sensitive than CSF Aβ42 at milder AD stages, and FDG-PET closely follows MRI biomarkers performance in predicting clinical changes.  **Objective:** to compare the sensitivity and specificity of individual AD biomarkers to predict progression from MCI to AD dementia in two different cohorts.  **Conclusion**  “Current findings suggest that CSF Abeta42 concentrations and hippocampal volumes may be used in combination to best identify prodromal AD.” | |
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| **Schmand 2012** | |
| **Patient sampling** | Study design: retrospective analysis of longitudinal data from ADNI database  175 MCI participants’ data, available for all measures of interest, were selected from the ADNI.  Exclusion criteria: people who used antidepressant medications with anti-cholinergic properties or those who used drugs with narcotic properties were excluded, but use of estrogens, cholinesterase inhibitors, or vitamin E was allowed if the dose remained stable. |
| **Patient characteristics and settings** | 89 MCI ADNI participants diagnosed by the Petersen 2010 criteria who had a ¹⁸F-FDG scan at baseline were included in the study. Demographic data reported on total sample (175 MCI).  Gender: converters: 31 women, 50 men; non-converters: 30 women, 64 men  Age (y): converters: 74.4 ± 7.4; non-converters: 74.1 ± 7.6  APOE ɛ4: not reported  MMSE: converters: 26.6 ± 1.8; non-converters: 27.2 ± 1.7  Education (y): converters: 15.6 ± 3.0; non-converters: 15.8 ± 3.9  Sources of referral: not reported  Sources of recruitment: multicenter |
| **Index test** | ¹⁸F-FDG PET scan  *Acquisition*  Not escribed. 18F-FDG PET scan data are provided by ADNI.  *Data analysis*  Using ¹⁸F-FDG acquired, controlled, and analyzed according to the ADNI protocol, ROI approaches (UC Berkeley) resulted in a set of 5 regions located in right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus. Because these ROIs were highly correlated (Jagust 2010), we averaged them across participants. This composite ROI was used in the present analyses.  Threshold: was based on the predicted probability of conversion to dementia as obtained from a logistic regression analysis with conversion as dependent variable and the rCGM of the ROI, described in the paper as the predictor. If this predicted probability was > 0.5, the ¹⁸F-FDG was considered positive. This corresponds to a rCGM value of < 1.20; pre-specified (Dr. Schmand email on 13th August 2013). |
| **Target condition** | Target condition: conversion from MCI to Alzheimer's disease dementia  Reference standard: NINCDS/ADRDA criteria of probable ADD (including a MMSE score between 20 and 26, and a CDR score of at least 0.5).  Unclear whether clinicians conducting follow-up were aware of the ¹⁸F-FDG results. |
| **Flow and timing** | Duration of follow-up: mean: 2.7 ± 0.9 years; range: 0.5 - 4.6 years  Information from the author:  At baseline: 18 participants with ¹⁸F-FDG test positive tests; 71 participants with ¹⁸F-FDG negative tests  At follow-up: 18 with abnormal ¹⁸F-FDG PET scan: 9 MCI-converters (MCI-ADD) and 9 MCI-non-converters (MCI-MCI); 71 with normal ¹⁸F-FDG PET scan: 29 MCI-converters (MCI-ADD) and 42 MCI-non-converters (MCI-MCI)  Number included in analysis: 89  TP = 9; FP = 9; FN = 29; TN = 42  Sensitivity=24%; specificity=82%  Loss to follow-up: none |
| **Notes**  We contacted the trial investigators contacted who provided relevant data tor the 2 x 2 table to be completed (Dr. Schmand’s email on 13th August 2013)  **Objective:** to examine the value of neuropsychological assessment, structural MRI, CSF biomarkers, and FDG PET scanning with respect to prediction of MCI to AD.  ***Hypothesis:***CSF biomarkers and FDG PET would lose prognostic value when applied in patients older than 75, whereas MRI and neuropsychological testing would not.  **Conclusion**  “The diagnostic yield of different techniques in predicting conversion from MCI to AD is moderate, and that it is affected by age of the subject under study. MRI and neuropsychological assessment remain informative in patients older than 75 years, unlike CSF biomarkers.” | |
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| **Shaffer 2013** | |
| **Patient sampling** | Study design: nested case-control design; retrospective analysis of longitudinal data from ADNI database  Method: Eight models were considered, including participants with all combinations of MR imaging, PET, and CSF markers with the covariates. We included only data for the accuracy of 18F-FDG PET alone provided by Dr Petrella (email on 21/3/2016)  Exclusion criteria: not reported in the paper; authors refer to Appendix E1 [online] |
| **Patient characteristics and settings** | 97 ADNI participants with MCI: 43 MCI-AD-converters; 54 MCI-non-converters (Table 1, p586).  Gender: women 14 and men 29 MCI converters; women 16 and men 38 non-MCI converters  Age(y): MCI converters 75.44±7.222; non-MCI converters 74.74± 1.185  APOE ε4 carrier: MCI converters 26/43 (60.47%); non-MCI converters 27/54 (50.00%)  MMSE: MCI converters 26.63±1.705; non-MCI converters 27.54±1.575  Education (y): MCI converters 16.33±2.579; non-MCI converters 15.54±3.184  Sources of referral: not reported  Setting: multicenter |
| **Index test** | 18F-FDG PET scan  *Acquisition*  Not described. FDG PET scan data are provided by ADNI.  *Data analysis*  FDG PET images were co-registered, averaged, reoriented, intensity corrected,and smoothed. The loading parameters for all components were analyzed by group (converters vs non-converters) by using an independent component analysis (ICA) (*t* test) to determine which 18F-FDG PET componentswere associated with conversion to AD.  Threshold: *“it is a weighted combination of loading parameters for about 5 different AD-specific metabolic patterns, and therefore is not a specific SUV value that can be directly compared with other studies; we sought to optimize accuracy”* (Dr Petrella; email on 21/3/2016) |
| **Target condition** | Target condition: conversion from MCI to AD  Reference standard: not reported |
| **Flow and timing** | Duration of follow-up: 4 years  Number included in analysis (N=97)  At follow-up: 43 MCI-AD (disease positive); 54 MCI-MCI (disease negative)  Conversion from MCI to ADD  18F-FDG PET scan alone  Sensitivity=88%%; specificity=76% (Dr Petrella’s email on 21/3/2016)  TP=38; FP=13; FN=5; TN=41; PPV=79.5%; NPV=85% (Calculated in Revman5)  18F-FDG PET scan & covariates (age, education, APOE genotype and ADAS-COG)  Sensitivity=81%%; specificity=83% (Dr Petrella; email on 21/3/2016)  TP=35; FP=9; FN=8; TN=45; PPV=74.5%; NPV=89% (Calculated in Revman5) |
| **Notes**  We contacted the trial investigators contacted who provided relevant data tor the 2 x 2 table to be completed (Dr Petrella’s email on 21/3/2016)  **Objective:** to assess the extent to which multiple AD biomarkers, *such as CSF proteins, MR imaging, and* 18F-FDG PET*,* improve the ability to predict future decline in participants with MCI compared with prediction based on clinical parameters alone; *to* develop the best model that could differentiate subjects with MCI who converted to AD from those who did not.  **Conclusion**  “Imaging and CSF biomarkers can improve prediction of conversion from MCI to AD compared with baseline clinical testing. Among three imaging and molecular biomarkers, FDG PET appears to be the primary contributor, with misclassification rates for FDG PET, MRI imaging, and CSF compared with clinical variables alone of 27.2% (p = 0.00001), 39.2% (p = 0.08), and 39.6% (p = 0.32), respectively. FDG PET appears to add the greatest prognostic information. Combining routine clinical and cognitive measures (age, education, ApoE ε4 and cognitive tests) with these biomarkers yields the highest accuracy (AUC=92%) for predicting conversion to AD in subjects with MCI; however, of these three biomarkers, FDG PET was the only biomarker that significantly improved the predictive value of clinical testing (87%), suggesting that the benefit of additional diagnostic tests is unclear”.  Important: the authors stated that *“further validation, standardization, and cost-effectiveness studies are needed to translate the most useful biomarkers into routine clinical practice*” | |
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| **Toussaint 2012** | |
| **Patient sampling** | Study design: nested cross-sectional study; retrospective analysis of longitudinal data from ADNI database  Participants with AD, MCI-converters and MCI-non-converters and normal elderly were recruited from ADNI cohort. The diagnostic groups were matched for age, sex and MMSE scores. We only included data on performance of the index test to discriminate between patients with MCI who convert to dementia and those who remained stable.  Exclusion criteria: not reported |
| **Patient characteristics and settings** | 80 MCI patients diagnosed by Petersen 2010 criteria: 40 MCI-converters; 40 MCI non-converters  Gender: MCI converters 15 women and 25 men; MCI non-converters 9 women and 31 men  Age (y): MCI converters 76±4.1 (range 70.2-86); non-MCI converters 76±4.2 (range 70.2-86)  APOE ε4 carrier: not reported  MMSE: MCI converters 26.8±1.7; non-MCI converters 27.5±1.8  Education (y): MCI converters 16.4±2.5; non-MCI converters 14.9±3.2  Sources of referral: not reported  Setting: multicenter |
| **Index test** | 18F-FDG PET scan  *Acquisition*  All baseline PET scans were acquired according to one of three different standardized protocols: 1) dynamic 30-min, six frame (5 min each) acquisitions starting 30 min post 18F-FDG injection, 2) quantitative 60-min dynamic protocol with continuous scanning from injection time to calculate absolute glucose metabolic rate using an arterial input function measured in the carotid, and 3) a single-frame 30-min acquisition starting 30 min post-injection for scanners without dynamic capability.  *Data analysis*  Spatial normalization of all images involved a 12-parameter affine transformation, followed by nonlinear iterative spatial transformation as provided in SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm/). voxel-wise t statistics for between group comparisons were compute using procedures in SPM5  Threshold:  Visual interpretation using­ SPM t-map; selected region: parietal left, temporal left/right and par-hippocampal left |
| **Target condition** | Target condition: conversion from MCI to Alzheimer’s disease dementia  Reference standard: NINCDS-ADRDA |
| **Flow and timing** | Duration of follow-up: 18 months  Number included in analysis (N=80)  At follow-up: 40 MCI-AD (disease positive); 40 MCI-MCI (disease negative  Conversion from MCI to ADD  Sensitivity=85%; specificity=75% for 18F-FDG PET alone (Table 3, p944)  TP=34; FP=10; FN=6; TN=30; PPV=77%; NPV=83% (Calculated in Revman5) |
| **Notes**  The author contacted, and confirmed that the information in Table 3 (sensitivity=85%; specificity=75%), p944 relates to 80 MCI; they also stated that they applied a quantitative analytical approach. (Dr Toussaint’s email on 12/3/2016)  **Objective:** to develop a multimodality classification tool for early diagnosis of AD based on imaging biomarkers derived from FDG-PET data spatial patterns (using t-test and ICA) combined with biological measurements (Apolipoprotein E) as well as scores from neuropsychological tests (MMSE, ADAS, and ADAS-cog).  ***Hypothesis***: glucose metabolic patterns observed in late stages of AD are already present at the prodromal stage  **Conclusion**  “Our approach achieved improved early detection and differentiation of typical versus pathological metabolic patterns in the MCI population, reaching 80% accuracy (85% sensitivity and 75% specificity) when using selected regions. The method has the potential to assist in the advance diagnosis of Alzheimer's disease and to identify early in the development of the disease those individuals at high risk of rapid cognitive decline who could be candidates for new therapeutic approaches…” When FDG-PET used in combination with cognitive scores, the accuracy was slightly improved, 82% (85% sensitivity and 80% specificity). | |
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| **Trzepacz 2014** | |
| **Patient sampling** | Study design: nested case-control study; retrospective analysis of longitudinal data from ADNI database  Exclusion criteria: not reported |
| **Patient characteristics and settings** | 50 MCI patients diagnosed by Albert 2011  Gender: 17 women, 33 men  Age (y): MCI converters 75.4 ±6.6 (range 59.6-83.9); non-MCI converters 74.2 ±8.4 (range 56.4-87.7)  APOE carrier: MCI converters 7/20 ε3/ε3, 10/20 ε3/ε4, 2/20 ε4/ε4 and 1/20 ε2/ε4; non-MCI converters 15/30 ε3/ε3, 11/30 ε3/ε4, 2/30 ε4/ε4 and 2/30 ε2/ε4  MMSE: MCI converters 26.2±2.1 (range 22-30); non-MCI converters 28.3±1.6 (range 24-30)  Education (y): MCI converters 16.3±2.8 (range 12-2); non-MCI converters 15.9±2.6 (range 12-20)  Sources of referral: not reported  Setting: multicenter |
| **Index test** | 18F-FDG PET scan  Information about the acquisition and data analysis not reported; it can be found in the ADNI procedure manual (http://www.adni-info.org/Scientists/ Pdfs/adniproceduresmanual12.pdf  Threshold: not reported; The cerebral metabolic rate of glucose in particular brain regions was assessed (Table 1, pg 145), a number of ROI, i.e., frontal, parietal and temporal cortices; posterior cingulate |
| **Target condition** | Target condition: conversion from MCI to Alzheimer’s disease dementia  Reference standard: NINCDS-ADRDA and DSM-IV criteria |
| **Flow and timing** | Duration of follow-up: 2 years  Number included in analysis (N=50)  At follow-up: 20 MCI-AD (disease positive); 30 MCI-MCI (disease negative)  Conversion from MCI to ADD  Sensitivity=10%; specificity=97% (Fig 2, p147)  TP=2; FP=1; FN=18; TN=29; PPV=67%; NPV=62% (Calculated in Revman5) |
| **Objective:** to compare the accuracy of 11C-PIB PET, 18F-FDG PET and MRI for the prediction of conversion from MCI to AD dementia at 2 year follow-up. In this systematic review we only consider the data for 18F-FDG PET scan.  **Conclusion**  Multivariate modelling found that among individual modalities, MRI had the highest predictive accuracy (67%) which increased by 9% to 76% when combined with PIB-PET, producing the highest accuracy among any biomarker combination. Individually, 11C-PIB PET generated the best sensitivity, and 18F-FDG PET had the lowest. Among individual brain regions, the temporal cortex was found to be most predictive for MRI and 11C-PIB PET. | |
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| **Young 2013** | |
| **Patient sampling** | Study design: nested case-control design; retrospective analysis of longitudinal data from ADNI database  MCI patients were recruited from ADNI cohort. Sampling process not described  Exclusion criteria: not reported |
| **Patient characteristics and settings** | 143 MCI patients diagnosed by Petersen 2010 criteria  Gender: MCI converters 17 women and 30 men; MCI non-converters 34 women and 62 men  Age (y): MCI converters 74.5±7.4; non-MCI converters 75.6±7.0  APOE ε4 carrier: not reported  MMSE: not reported  Education (y): not reported  Sources of referral: not reported  Setting: multicentre (across the U.S. and Canada) |
| **Index test** | 18F-FDG PET scan  *Acquisition*  All images were taken from the baseline scan for each included participants. Images were acquired by scanning 30–60 min post injection using scanner-specific protocols.  *Data analysis*  Gaussian process (GP) classification; Support vector machine (SVM) classification  Threshold: not reported |
| **Target condition** | Target condition: conversion from MCI to Alzheimer’s disease dementia  Reference standard: NINCDS-ADRDA and DSM-IV criteria |
| **Flow and timing** | Duration of follow-up:  Number included in analysis (N=143)  At follow-up: 47 MCI-AD (disease positive); 96 MCI-MCI (disease negative)  Conversion from MCI to ADD  Gaussian process (GP) classification (Table 5, p741):  Sensitivity=66%; specificity=64.6%  TP=31; FP=34; FN=16; TN=62; PPV=48%; NPV=79% (Calculated in Revman5)  SVM classification (Table 6, p741)  Sensitivity=55.3%; specificity=71.1%  TP=26; FP=22; FN=21; TN=74; PPV=54%; NPV=78% (Calculated in Revman5) |
| **Notes**  **Objective:** to evaluate the accuracy of multimodal probabilistic prediction of conversion to AD dementia in patients with MCI  **Conclusion**  “*Multimodal Gaussian process (GP) classifiers can be successfully applied to the prediction of conversion to AD dementia in MCI patients. Prediction of conversion is significantly better for multimodal classification than for any single modality, and also better for GP to SVM classification, largely due to the GP’s superior ability to exploit multimodal data”* (p744)*.*  A clear advantage can be seen both for multimodal classification and for the use of GP classification over the more widely used SVM. | |

ADNI, Alzheimer’s disease Neuroimaging Initiative; 18F-FDG PET, Fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography; MCI, mild cognitive impairment; AD, Alzheimer’s disease; APOE, **apolipoprotein E; MMSE, Mini-Mental State Examination;** NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; AUC, area under curve; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; HCI, hypometabolic convergence index; ADD, Alzheimer’s disease dementia; PALZ, Probability of ALZheimer; ROI, region of interest; SPM, statistical parametric map; rCGM, Regional cerebral glucose metabolism

\*Study also included in the meta-analysis

Notes: The objectives in ADNI studies differ. All ADNI studies assessed the accuracy of 18F-FDG PET as a single test and/or in combinations with a variety of biomarkers and neuropsychological tests for the prediction of MCI conversion to AD; two studies evaluated and validated a voxel-based analysis method of 18F-FDG PET imaging for conversion to AD (52, 61]; one study examined a 18F-FDG PET score as a biomarker for progression in MCI and AD [75]; one study compared the predictive accuracy of individual biomarkers, 18F-FDG PET, MRI and CSF tests, in two different cohort [64]; one study [66] assessed whether combined MRI, 18F-FDG PET scan and CSF biomarkers can improve prediction of conversion from MCI to AD when compared with ‘routine clinical test’, which comprised the baseline clinical and cognitive measures (cognitive tests, age, education, and ApoE).