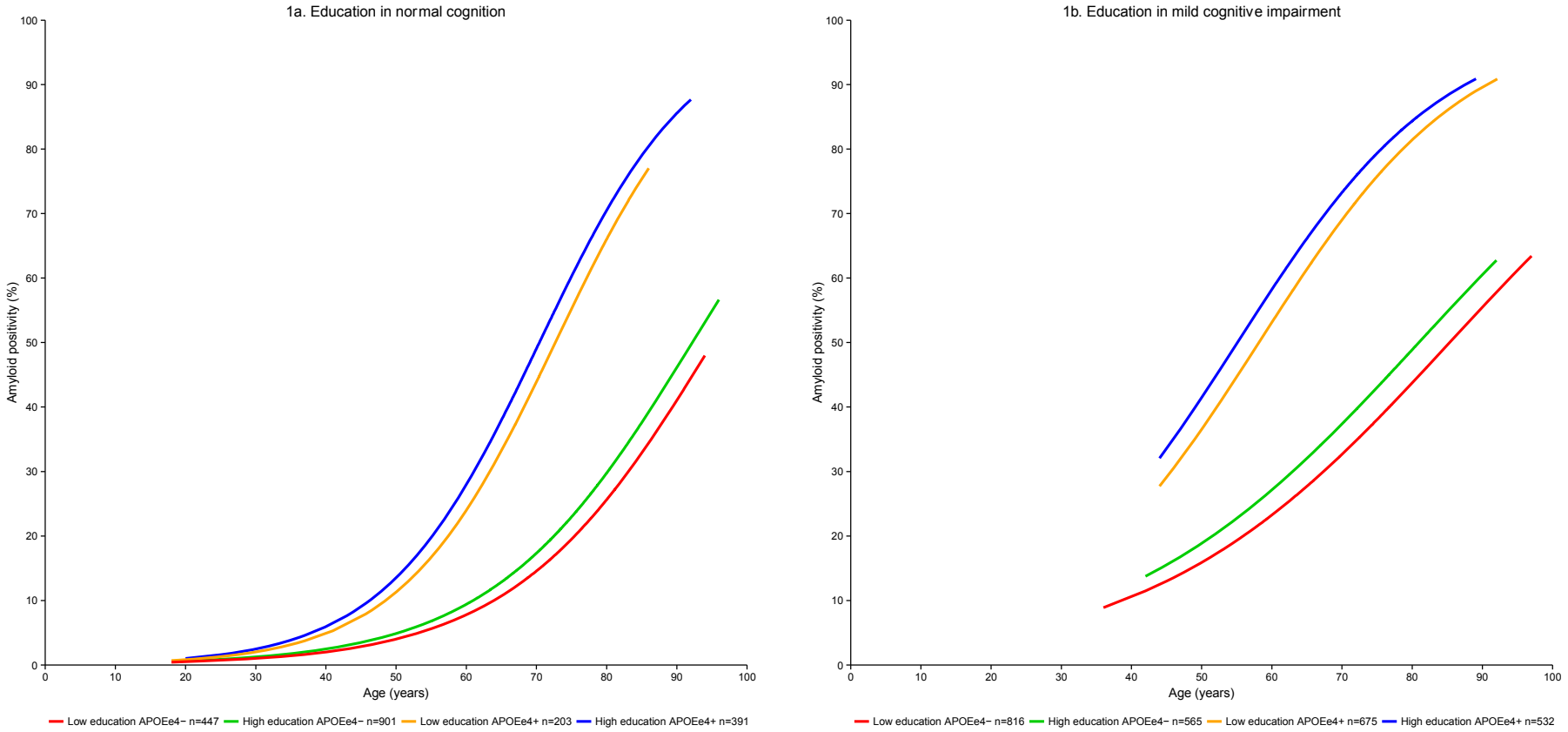
Supplementary Online Content

Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. doi:10.1001/jama.2015.4668.

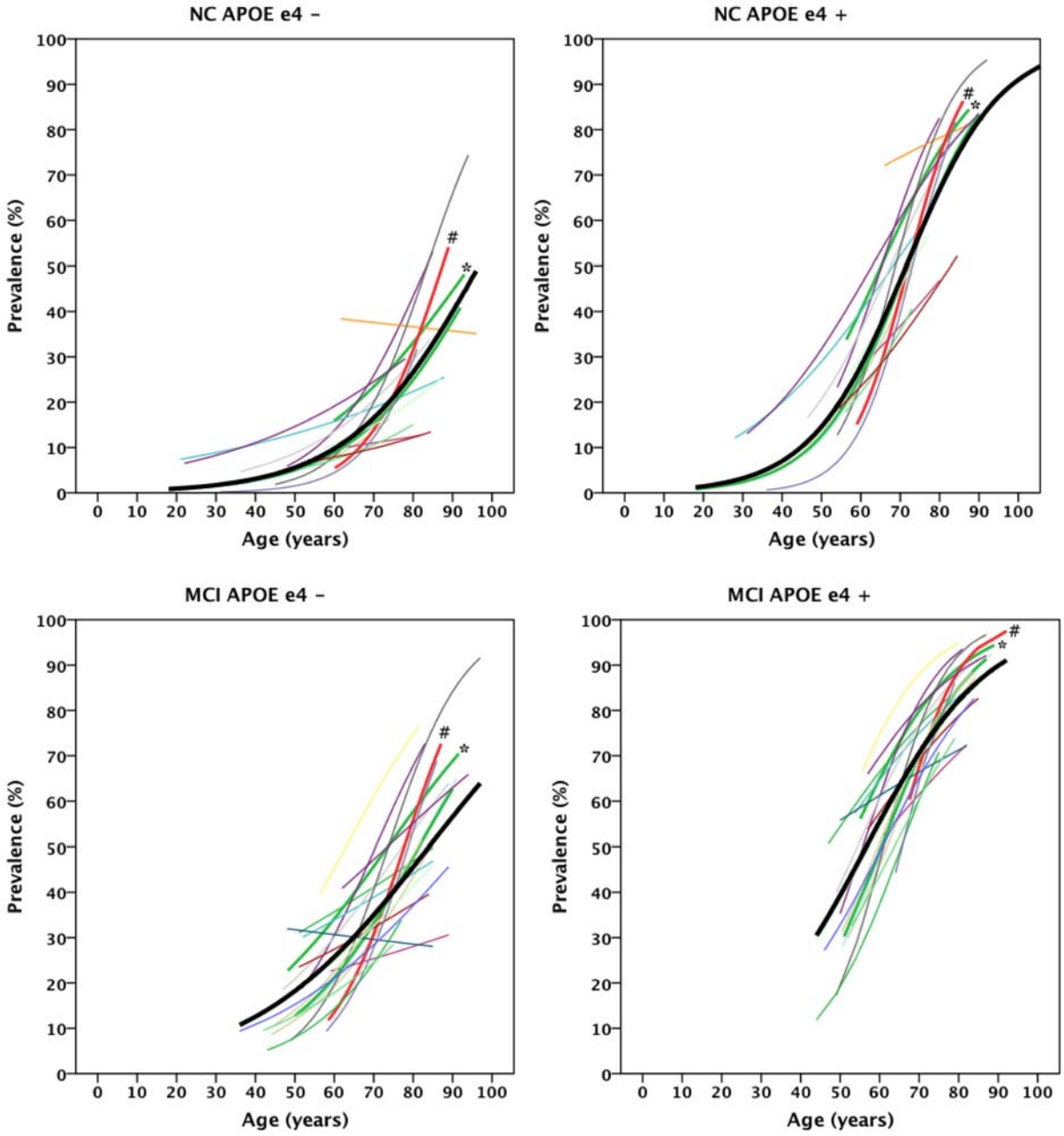
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Prevalence of amyloid positivity according to educational level



APOE=apolipoprotein E.
Panel A shows prevalence estimates of amyloid positivity in participants with normal cognition and panel B in participants with mild cognitive impairment according to education (above/below median) and *APOE*-ε4 carrier status. The model for Panel A and B included age, cognitive status, *APOE*-ε4 status, education, an interaction between age and cognitive status, and between age and *APOE*-ε4 status as predictors.

eFigure 2. Prevalence estimates of amyloid positivity in individual studies with more than 50 participants according to cognitive status and *APOE*-ε4 carrier status



# ADNI study. * AIBL study. The bold line indicates the total group average and is also shown in Figure 3 of the main text.
NC=normal cognition. MCI=mild cognitive impairment. *APOE*=apolipoprotein E.
The prevalence estimates were generated from generalized estimating equations models.
Panel A shows prevalence estimates of amyloid positivity for *APOE*-ε4 negative participants with NC (n=1489 from 17 studies). Panel B shows prevalence estimates of amyloid positivity for *APOE*-ε4 positive participants with NC (n=637 from 17 studies). Panel C shows prevalence estimates of amyloid positivity for *APOE*-ε4 negative patients with MCI (n=1518 from 21 studies) Panel D shows prevalence estimates of amyloid positivity for *APOE*-ε4 positive patients with MCI (n=1360 from 21 studies).

eTable 1a. Quality rating

		STROBE/QUADAS criterion*									
Study	**Reference(s)**	**Setting**	**Generalizability**	**Selection**	**Measurements**	**Reference**	**Bias**	**Subject flow**	**Descriptives**	**Outcome**	**Dichotomization**
Amsterdam	[1]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	[2]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	[3]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Antwerp	[4]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	[5]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Athens	[6]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Barcelona HSP	[7]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Barcelona CUH	[8]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Berkeley	[9]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Bremen	[10]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Brescia	[11]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Brussels	[12]	yes	yes	yes	yes	yes	yes	n.a.	yes	yes	yes
Caen	[13]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
	[14]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Chandigarh	[15]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Coimbra	[16]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Copenhagen	[17]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Dallas	[18]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Freiburg	[19]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes

Study	Reference(s)	Setting	Generalizability	Selection	Measurements	Reference	Bias	Subject flow	Descriptives	Outcome	Dichotomization
Gothenburg	[20]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Gothenburg	[21]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Hong Kong	[22]	yes	yes	yes	yes	yes	yes	n.a.	yes	yes	yes
Krakow	unpublished										
Lausanne	[23]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Leuven	[24]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
	[25]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Lisbon	unpublished										
Ljubljana	unpublished										
Lorenskog	[26]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Madrid	[27]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Mannheim	[28]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Melbourne	[29]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
	[30]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
	[31]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Lisbon	unpublished										
Ljubljana	unpublished										
Munich TU	[32]	yes	yes	yes	yes	yes	n.a.	n.a.	yes	yes	yes
	[33]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Nijmegen	[34]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Paris	[35]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Pennsylvania	[36]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes

Study	Reference(s)	Setting	Generalizability	Selection	Measurements	Reference	Bias	Subject flow	Descriptives	Outcome	Dichotomization
Perugia	[37]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Perugia	[38]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Philadelphia	[39]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Phoenix	[40]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Pittsburgh	[41]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
	[42]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
San Francisco	[43]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
	[44]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Santander	[45]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Scinawa	unpublished										
Seoul NUH	[46]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Seoul SMC	[47]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Stockholm	[48]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
St. Louis	[49]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Thessaloniki	[50]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Tours	[13]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Turku	[51]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Warsaw	unpublished										
ADNI	[52]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
AIBL	[53]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Avid	[54]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
DESCRIPA	[55]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

* The quality of the primary paper(s) from studies that provided participant level data was assessed using STROBE and QUADAS items (see below for detailed explanation). n.a.=not available.

Study	Reference(s)	Setting	Generalizability	Selection	Measurements	Reference	Bias	Subject flow	Descriptives	Outcome	Dichotomization
DCN	[28]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
EDAR	unpublished										
FBB phase 2	[56]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
LeARN	[2]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	[57]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes
Mattsson	[58]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
UK/Turku	[59]	yes	yes	yes	yes	yes	n.a.	yes	yes	yes	yes

eTable 1b. Quality checklist of STROBE and QUADAS items

Criterion	STROBE[60] item(s)	QUADAS[61] item(s)	Operationalization
Setting	5		Description of study setting and recruitment strategy.
Generalizability		1	Representativeness of spectrum of participants who will receive the test in practice or in research projects.
Selection	6	2	Description of inclusion criteria and sampling method.
Measurements	7, 8, 11	8, 9	Detailed description of amyloid assessment method and diagnostic criteria.
Reference		3	Appropriate method of amyloid assessment.
Bias	9	7, 10, 11	Indication that the clinician responsible for the clinical diagnosis was blinded for amyloid status, and that amyloid measurements were interpreted independent of risk factors.
Subject flow	13	5, 6, 13, 14	Explanation of non-participation at each stage.
Descriptives	14	1	Characterization of participants.
Outcome	15		Report of prevalence data.
Dichotomization	16	8, 9	Description of cutoff for amyloid positivity.

STROBE=strengthening the reporting of observational studies in epidemiology. QUADAS=quality assessment of studies of diagnostic accuracy.
Each criterion was rated “yes” when criterion was met, not available (n.a.) when not reported and “no” when criterion was not met.

eTable 2. PET measurement details

Study	Tracer	Outcome	Acquisition interval	Cutoff
ADNI	Florbetapir PiB	SUVr	50-70 min	1.11 1.114
Amsterdam	PiB	BP_{ND} SUVr	0-90 min 60-90 min	Visual read
AIBL	PiB	SUVr	40-70 min	1.5
Avid	Florbetapir	SUVr	50-60 min	Visual read
Berkeley	PiB	DVR	0-90 min	1.08
Caen	Florbetapir	SUVr	50-70 min	1.1
Copenhagen	PiB	SUVr	40-70 min	1.5 and visual read
Dallas	Florbetapir	SUVr	50-60 min	1.22
FBB phase 2	Florbetaben	BAPL on visual read	90-110 min	1 BAPL (no amyloid load)
Freiburg	PiB	BP_{ND}	0-90 min	Visual read
Hong Kong	PiB	SUVr	35-45 min	1.46 and visual read
LeARN	PiB	BP_{ND} SUVr	0-90 min 60-90 min	Visual read
Leuven	Flutemetamol PiB	SUVr DVR	85-115 min 40-70 min	Visual read
Melbourne	Florbetaben PiB	SUVr DVR	90-110 min 0-90 min	1.4/1.45 Visual read
Munich TU	PiB	SUVr	40-70 min	Visual read
Paris	PiB	SUVr	50-70 min	1.4
Pennsylvania	PiB	SUVr	50-70 min	1.15
Philadelphia	Florbetapir	SUVr	50-60 min	Visual read
Phoenix	Florbetapir	SUVr	50-60 min	1.08

Study	Tracer	Outcome	Acquisition interval	Cutoff
Pittsburgh	PiB	SUVr	50-70 min	1.67 (atrophy corrected)
San Francisco	PiB	DVR	0-90 min	Visual read
Santander	PiB	SUVr	55-60 min	Visual read
Seoul NU	PiB	SUVr	60-90 min	1.5
Seoul SMC	PiB	SUVr	60-90 min	1.5
Stockholm	PiB	SUVr	40-60 min	1.5
St. Louis	PiB	MCBP	30-60 min	0.18
Tours	Florbetapir	SUVr	50-60 min	Visual read
Turku	PiB	SUVr	60-90 min	1.5
UK/Turku	PiB	SUVr	60-90 min	> 2 SD controls

PET=positron emission tomography. PiB=Pittsburgh compound B. SUVr=standardized uptake value ratio. DVR=distribution volume ratio. BP_{ND}=nondisplaceable binding potential. BAPL=brain amyloid-β plaque load. MCBP=mean cortical binding potential.

eTable 3. CSF measurement details

Study	Assay	Cutoff $A\beta_{1-42}$ (pg/ml)
ADNI	Luminex®	192
Amsterdam	Innotest®	550
Antwerp	Innotest®	638.5
Athens	Innotest®	490
Barcelona CUH	Innotest®	500
Barcelona HSP	Innotest®	550
Bremen	Innotest®	450
Brescia	Innotest®	500
Brussels	Innotest®	430
Chandigarh	Innotest®	662.65
Coimbra	Innotest®	542
DCN	Innotest®	600
DESCRIPA	Innotest®	550
EDAR	Luminex®	389
Gothenburg	Innotest®	450
Krakow	Innotest®	380
Lausanne	Innotest®	550
LeARN	Innotest®	550
Lisbon	Innotest®	445
Ljubljana	Innotest®	450
Lorenskog	Innotest®	550
Madrid	Innotest®	550
Mannheim	Innotest®	450
Mattsson	Innotest®	482
Nijmegen	Innotest®	500
Perugia	Innotest®	550
Scinawa	Innotest®	600

Study	Assay	Cutoff $A\beta_{1-42}$ (pg/ml)
Stockholm	Innotest®	550
St. Louis	Innotest®	459
Thessaloniki	Innotest®	450
Warsaw	Innotest®	610

Assays: ELISA (INNOTEST® β-amyloid$^{1-42}$) or Luminex xMAP® technology (Fujirebio Europe, Zwijndrecht, Belgium)

eTable 4. Comparison of in- and excluded studies

Characteristics	**Included unique studies n=55**		**Excluded unique studies n=31***	
Publication years	2003-2015		1998-2013	
	Normal cognition	*MCI*	*Normal cognition/SCI*	*MCI*
Number of studies	40	47	28#	11#
Age, mean	66.8	70.2	68.3	70.1
Gender, mean	55.0	46.3	53.0	56.1
Education in years, mean	14.6	12.5	14.0	12.5
MMSE, mean	29.0	26.8	29.0	26.4
APOE-ε4 positive, %	29.5	47.1	26.6	40.6
Prevalence amyloid positive, %	23.1	48.7	27.1	44.8

*31 out of 36 excluded unique studies were published studies. # 8 studies published data on participants with normal cognition and MCI.
SCI=subjective cognitive impairment. MC=mild cognitive impairment.
Means and percentages of excluded unique studies are reported on study level using data directly available from the publications. Data were reported without distinguishing between participants with normal cognition or SCI in some studies and means and percentages for this group are therefore pooled in this Table.

eTable 5. Characteristics of included studies

Study	Reference(s)	Cognitive status	No. participants (biomarker)	Age (range)	No. *APOE*-ε4 + (%)	MMSE (SD)	Study setting
Amsterdam	[1, 2, 3]	Normal cognition	15 (PET)	67.0 (57.0-80.0)	3 (23)	28.4 (1.5)	Research
		SCI	251 (CSF)	64.1 (55.2-85.4)	91 (38)	28.4 (1.5)	Clinical
		MCI	251 (15 PET / 236 CSF)	68.9 (44.0-85.3)	129 (56)	26.5 (2.5)	Clinical
Antwerp	[4, 5]	Normal cognition	27 (CSF)	49.8 (22.0-90.0)	9 (33)	29.4 (1.4)	Research
		SCI	16 (CSF)	74.9 (54.0-87.0)	4 (31)	27.3 (1.8)	Clinical
		MCI	113 (CSF)	75.9 (47.0-94.0)	34 (39)	25.3 (3.0)	Clinical
Athens	[6]	Normal cognition	30 (CSF)	70.3 (42.0-86.0)	n.a.	28.9 (0.9)	Research
		SCI	1 (CSF)	65	n.a.	30	Clinical
		MCI	29 (CSF)	66.8 (40.0-82.0)	n.a.	25.7 (1.4)	Clinical
Barcelona HSP	[7]	Normal cognition	66 (CSF)	60.6 (45.5-77.5)	16 (25)	29.0 (1.1)	Research
		SCI	29 (CSF)	62.7 (44.0-76.0)	6 (21)	28.7 (1.2)	Clinical
		MCI	84 (CSF)	67.5 (45.0-83.4)	32 (39)	27.4 (1.9)	Clinical
Barcelona CUH	[8]	Normal cognition	41 (CSF)	64.1 (48.0-85.0)	7 (17)	28.6 (1.2)	Research
		SCI	53 (CSF)	64.1 (45.0-80.0)	16 (31)	28.2 (1.6)	Clinical
		MCI	65 (CSF)	69.9 (50.0-83.0)	24 (38)	25.0 (3.0)	Clinical

Study	Reference(s)	Cognitive status	No. participants (biomarker)	Age (range)	No. *APOE*-ε4 + (%)	MMSE (SD)	Study setting
Berkeley	[9]	Normal cognition	81 (PET)	75.0 (61.0-96.0)	21 (28)	29.0 (1.2)	Research
Bremen	[10]	MCI	34 (CSF)	68.1 (53.0-86.0)	n.a.	26.4 (2.6)	Clinical
Brescia	[11]	Normal cognition	81 (CSF)	52.9 (21.0-88.0)	16 (20)	29.4 (0.9)	Research
		MCI	126 (CSF)	70.6 (52.0-85.0)	42 (40)	25.5 (2.6)	Clinical
Brussels	[12]	Normal cognition	51 (CSF)	64.6 (50.0-86.0)	n.a.	n.a.	Research
		SCI	29 (CSF)	65.2 (51.0-80.0)	0 (0)	28.5 (1.0)	Clinical
		MCI	51 (CSF)	71.1 (57.0-84.0)	4 (67)	27.1 (1.8)	Clinical
Caen	[13, 14]	Normal cognition	81 (PET)	53.7 (21.0-84.0)	17 (26)	29.2 (0.8)	Research
		SCI	14 (PET)	68.4 (57.0-83.0)	1 (11)	28.7 (1.0)	Clinical
		MCI	23 (PET)	73.7 (58.0-86.0)	7 (41)	26.5 (2.5)	Clinical
Chandigarh	[15]	Normal cognition	44 (CSF)	60.8 (38.0-84.0)	0 (0)	n.a.	Research
Coimbra	[16]	MCI	60 (CSF)	69.4 (48.0-85.0)	47	26.7 (2.7)	Clinical
Copenhagen	[17]	Normal cognition	18 (PET)	61.4 (51.5-74.8)	n.a.	29.4 (1.1)	Mixed
		SCI	3 (PET)	66.6 (47.9-82.6)	n.a.	25.7 (2.5)	Clinical
		MCI	6 (PET)	64.9 (54.9-81.0)	n.a.	26.1 (2.6)	Clinical
Dallas	[18]	Normal cognition	106 (PET)	71.3 (54.5-84.5)	28 (24)	n.a.	Research

Study	Reference(s)	Cognitive status	No. participants (biomarker)	Age (range)	No. *APOE*-ε4 + (%)	MMSE (SD)	Study setting
Freiburg	[19]	MCI	13 (PET)	69.9 (62.1-77.8)	n.a.	25.1 (2.8)	Clinical
Gothenburg	[20, 21]	Normal cognition	54 (CSF)	66.7 (52.0-80.0)	17 (31)	29.3 (1.1)	Research
		SCI	59 (CSF)	61.4 (49.0-79.0)	24 (41)	29.3 (0.9)	Clinical
		MCI	89 (CSF)	61.5 (42.0-79.0)	44 (49)	28.3 (1.4)	Clinical
Hong Kong	[22]	Normal cognition	18 (PET)	67.2 (56.0-84.0)	n.a.	28.7 (1.4)	Research
Krakow	unpublished	Normal cognition	5 (CSF)	69.4 (64.0-81.0)	1 (20)	27.8 (2.2)	Research
		MCI	12 (CSF)	74.1 (63.0-81.0)	1 (8)	27.4 (2.9)	Clinical
Lausanne	[23]	Normal cognition	14 (CSF)	66.4 (55.0-76.0)	4 (44)	28.8 (1.3)	Research
		SCI	9 (CSF)	70.1 (55.0-78.0)	2 (33)	28.9 (0.9)	Clinical
		MCI	68 (CSF)	73.7 (53.0-87.0)	8 (44)	26.5 (3.1)	Clinical
Leuven	[24, 25]	Normal cognition	41 (PET)	62.0 (25.0-89.0)	3 (19)	29.0 (1.0)	Research
		MCI	20 (PET)	72.7 (57.0-83.0)	n.a.	28.0 (0.9)	Clinical
Lisbon	unpublished	SCI	3 (CSF)	60.0 (57.0-63.0)	n.a.	29.0 (1.0)	Clinical
		MCI	35 (CSF)	62.5 (45.0-82.0)	n.a.	27.3 (2.4)	Clinical
Ljubljana	unpublished	Normal cognition	10 (CSF)	67.9 (57.0-79.0)	n.a.	28.5 (1.3)	Research
		MCI	10 (CSF)	64.6 (53.0-74.0)	n.a.	28.0 (1.4)	Clinical

Study	Reference(s)	Cognitive status	No. participants (biomarker)	Age (range)	No. *APOE*-ε4 + (%)	MMSE (SD)	Study setting
Lorenskog	[26]	SCI	32 (CSF)	58.6 (43.0-78.0)	22 (69)	29.3 (0.7)	Clinical
	[26]	MCI	79 (CSF)	61.1 (43.0-77.0)	36 (46)	27.8 (1.5)	Clinical
Madrid	[27]	Normal cognition	60 (CSF)	67.7 (26.0-89.0)	n.a.	n.a.	Research
Mannheim	[28]	Normal cognition	23 (CSF)	66.9 (53.0-83.0)	n.a.	26.1 (3.0)	Research
		MCI	32 (CSF)	70.8 (56.0-86.0)	n.a.	27.5 (1.5)	Clinical
Melbourne	[29-31]	NC	33 (PET)	72.2 (56.0-83.0)	4 (18)	29.5 (0.7)	Research
		MCI	65 (PET)	72.1 (49.0-85.0)	12 (60)	26.9 (2.1)	Clinical
Munich TU	[32, 33]	Normal cognition	15 (PET)	64.2 (53.0-75.0)	8 (53)	29.3 (0.7)	Research
		MCI	14 (PET)	68.9 (50.0-78.0)	7 (50)	27.1 (2.4)	Clinical
Nijmegen	[34]	Normal cognition	13 (CSF)	66.0 (50.0-78.0)	2 (50)	27.5 (2.0)	Research
		MCI	27 (CSF)	72.1 (61.0-87.0)	8 (62)	26.9 (2.1)	Clinical
Paris	[35]	Normal cognition	11 (PET)	65.8 (58.6-75.4)	2 (25)	29.2 (1.0)	Research
		MCI	14 (PET)	69.5 (53.0-89.1)	4 (40)	24.4 (2.9)	Clinical
Pennsylvania	[36]	Normal cognition	14 (PET)	70.4 (59.0-87.0)	4 (31)	29.5 (0.5)	Research
Perugia	[37, 38]	Normal cognition	20 (CSF)	66.7 (55.0-79.0)	n.a.	28.6 (1.0)	Research
		SCI	38 (CSF)	67.5 (46.0-83.0)	n.a.	27.1 (1.4)	Clinical

Study	Reference(s)	Cognitive status	No. participants (biomarker)	Age (range)	No. *APOE*-ε4 + (%)	MMSE (SD)	Study setting
Perugia	[37, 38]	MCI	67 (CSF)	70.1 (50.0-81.0)	n.a.	24.2 (2.3)	Clinical
Philadelphia	[39]	Normal cognition	27 (PET)	65.3 (38.0-91.0)	n.a.	29.6 (0.7)	Mixed
Phoenix	[40]	Normal cognition	147 (PET)	44.9 (18.0-92.0)	39 (29)	29.7 (0.5)	Research
		MCI	53 (PET)	71.1 (50.0-90.0)	21 (40)	27.5 (1.8)	Clinical
Pittsburgh	[41, 42]	Normal cognition	165 (PET)	77.4 (39.0-94.0)	31 (21)	28.7 (1.4)	Research
		MCI	96 (PET)	75.6 (49.0-97.0)	37 (40)	26.9 (2.5)	Clinical
San Francisco	[43, 44]	Normal cognition	10 (PET)	61.7 (48.0-73.0)	1 (20)	29.6 (0.5)	Research
		MCI	18 (PET)	65.3 (42.0-85.0)	8 (57)	27.8 (2.0)	Clinical
Santander	[45]	Normal cognition	1 (PET)	58	0 (0)	30	Research
		SCI	2 (PET)	68.5	0 (0)	27.5	Clinical
		MCI	38 (PET)	66.5 (47.0-80.0)	9 (32)	26.8 (1.7)	Clinical
Scinawa	unpublished	Normal cognition	11 (CSF)	62.1 (56.0-73.0)	n.a.	29.6 (0.7)	Research
		SCI	5 (CSF)	57.0 (52.0-63.0)	n.a.	27.8 (3.0)	Clinical
		MCI	20 (CSF)	70.7 (58.0-80.0)	n.a.	25.6 (2.0)	Clinical
Seoul NUH	[46]	Normal cognition	35 (PET)	71.4 (62.0-82.0)	18 (50)	27.6 (1.9)	Research
		MCI	28 (PET)	70.8 (59.0-89.0)	14 (50)	23.3 (3.2)	Clinical

Study	Reference(s)	Cognitive status	No. participants (biomarker)	Age (range)	No. *APOE*-ε4 + (%)	MMSE (SD)	Study setting
Seoul SMC	[47]	MCI	113 (PET)	72.2 (51.0-85.0)	33 (29)	26.2 (2.8)	Clinical
Stockholm	[48]	MCI	19 (PET)	62.1 (50.7-74.6)	13 (68)	27.3 (2.5)	Clinical
St. Louis	[49]	Normal cognition	655 (145 PET / 510 CSF)	67.2 (37.3-91.1)	221 (34)	29.1 (1.2)	Research
		MCI	196 (37 PET / 159 CSF)	73.9 (50.6-91.0)	111 (57)	26.6 (2.8)	Clinical
Thessaloniki	[50]	MCI	8 (CSF)	75.0 (56.0-87.0)	0 (0)	25.4 (4.6)	Clinical
Tours	[13]	Normal cognition	21 (PET)	68.4 (60.0-109.0)	9 (45)	29.2 (0.7)	Research
		MCI	12 (PET)	73.7 (59.0-89.0)	5 (50)	25.8 (2.7)	Clinical
Turku	[51]	MCI	29 (PET)	71.0 (59.0-81.0)	16 (55)	27.3 (1.7)	Clinical
Warsaw	unpublished	Normal cognition	8 (CSF)	58.8 (51.0-73.0)	n.a.	28.1 (1.5)	Research
		SCI	22 (CSF)	61.2 (49.0-84.0)	n.a.	28.0 (2.2)	Clinical
		MCI	40 (CSF)	65.9 (49.0-83.0)	n.a.	28.0 (1.5)	Clinical
Multicenter study*	**Reference(s)**	**Cognitive status**	**No. participants (biomarker)**	**Age (range)**	**No. *APOE*-ε4 + (%)**	**MMSE (SD)**	**Study setting**
ADNI	[52]	Normal cognition	385 (116 PET / 269 CSF)	74.6 (56.3-93.0)	90 (27)	29.0 (1.2)	Research
		SCI	1 (CSF)	73.8	n.a.	28.0	Mixed
		MCI	706 (103 PET / 603 CSF)	72.8 (48.2-91.6)	339 (49)	27.8 (1.8)	Mixed
AIBL	[53]	Normal cognition	178 (PET)	72.1 (59.0-89.0)	72 (41)	28.8 (1.2)	Research

Multicenter study*	Reference(s)	Cognitive status	No. participants (biomarker)	Age (range)	No. *APOE*-ε4 + (%)	MMSE (SD)	Study setting
AIBL	[53]	MCI	56 (PET)	75.7 (58.5-92.1)	30 (54)	27.0 (2.2)	Clinical
Avid	[54]	MCI	146 (PET)	73.0 (54.0-96.0)	6 (23)	27.1 (3.0)	Clinical
DESCRIPA	[55]	SCI	59 (CSF)	66.0 (54.5-82.7)	29 (57)	28.8 (1.1)	Clinical
		MCI	85 (CSF)	69.5 (55.681.7)	38 (51)	26.2 (2.6)	Clinical
DCN	[28]	MCI	402 (CSF)	66.3 (36.0-89.0)	153 (42)	27.0 (2.3)	Clinical
EDAR	unpublished	Normal cognition	26 (CSF)	64.1 (41.0-87.0)	8 (40)	29.2 (0.9)	Research
		MCI	61 (CSF)	69.3 (44.0-87.0)	29 (54)	26.8 (2.5)	Clinical
FBB phase 2	[56]	Normal cognition	68 (PET)	68.2 (55.0-85.0)	n.a.	29.3 (0.8)	Research
LeARN	[2, 57]	SCI	50 (16 PET / 34 CSF)	64.3 (38.6-79.6)	7 (44)	28.2 (1.5)	Clinical
		MCI	67 (40 PET / 27 CSF)	67.2 (47.0-88.5)	23 (61)	27.0 (2.0)	Clinical
Mattsson	[58]	Normal cognition	202 (CSF)	64.6 (38.1-91.0)	27 (28)	28.9 (1.3)	Research
		SCI	21 (CSF)	60.1 (50.0-70.0)	9 (45)	29.1 (1.1)	Clinical
		MCI	352 (CSF)	68.8 (47.0-85.0)	156 (52)	26.2 (2.7)	Clinical
UK/Turku	[59]	MCI	31 (PET)	69.4 (43.0-80.0)	7 (41)	27.5 (1.5)	Clinical

SCI=subjective cognitive impairment. MCI=mild cognitive impairment. MMSE=mini mental state examination (range 0-30, with 30 as the best score). PET=positron emission tomography. CSF=cerebrospinal fluid. *APOE*=apolipoprotein E. n.a.=not available. HSP=hospital sant pau. CUH=clinic university hospital. TU=technical university. NUH=national university hospital. SMC=samsung medical center.
*Multicenter studies: Alzheimer disease neuroimaging initiative (ADNI), Australian imaging biomarker and lifestyle study (AIBL), Avid pharmaceuticals multicenter study, Development of screening guidelines and criteria for predementia Alzheimer disease (DESCRIPA), Dementia competence network (DCN), Beta amyloid oligomers in the early diagnosis of Alzheimer disease and as marker for treatment response (EDAR), Florbetaben (FBB) phase 2 multicenter study, Leiden - Alzheimer research Nederland (LeARN), Mattsson publication multicenter study, United Kingdom (UK)/Turku multicenter study.

eTable 6. Number needed to screen according to age, cognitive status and *APOE* genotype

Group	50 yr	60 yr	70 yr	80 yr	90 yr
Number needed to screen if *APOE* genotype is known					
Participants with normal cognition					
Total group	10.0 (7.7-12.5)	6.3 (5.3-7.7)	4.3 (3.7-5.3)	3.0 (2.6-3.6)	2.3 (2.0-2.7)
APOE-ε4-	16.7 (11.1-25.0)	10.0 (7.7-14.3)	5.9 (4.8-7.1)	3.6 (3.0-4.3)	2.4 (2.0-3.0)
APOE-ε4+	6.7 (4.8-10.0)	3.4 (2.7-4.5)	2.1 (1.9-2.4)	1.5 (1.4-1.6)	1.2 (1.1-1.3)
APOE-ε4ε4	2.8 (2.0-4.0)	1.7 (1.4-2.4)	1.3 (1.1-1.7)	1.1 (1.0-1.4)	1.0 (1.0-1.3)
Patients with MCI					
Total group	3.7 (3.3-4.3)	2.7 (2.4-3.0)	2.0 (1.9-2.2)	1.7 (1.5-1.8)	1.4 (1.3-1.5)
APOE-ε4-	5.3 (4.2-7.1)	3.8 (3.2-4.5)	2.9 (2.6-3.2)	2.2 (2.0-2.5)	1.8 (1.6-2.1)
APOE-ε4+	2.5 (2.1-3.0)	1.8 (1.6-2.0)	1.4 (1.4-1.5)	1.2 (1.2-1.3)	1.1 (1.1-1.2)
APOE-ε4ε4	1.6 (1.3-2.1)	1.3 (1.2-1.4)	1.1 (1.1-1.2)	1.1 (1.0-1.2)	1.0 (1.0-1.1)
Number of participants needed for *APOE* genotyping in order to find 1 amyloid positive participant *					
Participants with normal cognition					
APOE-ε4-	23.6 (15.8-35.5)	14.2 (10.9-20.3)	8.3 (6.8-10.1)	5.1 (4.3-6.2)	3.5 (2.8-4.3)
APOE-ε4+	22.6 (16.9-33.9)	11.7 (9.2-15.4)	7.1 (6.3-8.1)	5.0 (4.6-5.5)	4.1 (3.9-4.4)
APOE-ε4ε4	89.6 (64.5-129.0)	55.6 (45.4-76.8)	40.3 (35.8-54.7)	35.4 (32.9-43.6)	34.3 (32.6-41.4)
Patients with MCI					
APOE-ε4-	9.9 (7.9-13.5)	7.3 (6.1-8.6)	5.4 (4.8-6.1)	4.2 (3.7-4.7)	3.4 (3.0-3.9)
APOE-ε4+	5.3 (4.5-6.4)	3.8 (3.5-4.2)	3.0 (2.9-3.2)	2.6 (2.5-2.7)	2.4 (2.3-2.5)
APOE-ε4ε4	14.7 (12.3-19.7)	11.9 (11.1-13.1)	10.6 (10.0-11.6)	9.9 (9.6-11.0)	9.7 (9.5-10.6)

Data are number (95% confidence interval). MCI=mild cognitive impairment. *APOE*=apolipoprotein E.
Numbers needed to screen indicate the number needed to screen to find one amyloid positive participant. It is calculated as the inverse of the point estimates for the prevalence of amyloid pathology regardless of APOE genotype, according to *APOE*-ε4 carrier status or *APOE* ε4ε4 genotype. If no participants with the exact age were available, the prevalence estimate at the nearest age was used in the calculation.
* If *APOE* genotype is unknown, participants need to be screened for this first. The number needed to screen now indicate the number of participants for whom *APOE* genotyping needs to be performed in order to find one participant with that *APOE*-ε4 carrier status who is amyloid positive. It is calculated as the inverse of the point estimates for the prevalence of amyloid pathology multiplied by the *APOE*-ε4 background prevalence in our sample.

eTable 7. Heterogeneity assessment in aggregated data

Group	Measure	<50 yr	50-54 yr	55-59 yr	60-64 yr	65-69 yr	70-74 yr	75-79 yr	80-84 yr	≥85 yr
Normal cognition	I^2 (%)	7.5	0.0	0.0	19.1	0.0	12.7	0.0	15.5	18.9
APOE-ε4-	No. of studies	11	12	16	24	24	25	22	16	11
Normal cognition	I^2 (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.5	0.0
APOE-ε4+	No. of studies	7	10	17	19	20	19	13	12	9
SCI *APOE*-ε4-	I^2 (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	No. of studies	3	6	11	10	10	8	8	5	2
SCI *APOE*-ε4+	I^2 (%)	0.0	0.0	0.0	9.7	51.5*	0.0	0.0	2.6	-
	No. of studies	4	5	6	9	8	8	8	2	0
MCI *APOE*-ε4-	I^2 (%)	0.0	0.0	0.0	34.3	49.3	23.3	59.6*	34.1	32.8
	No. of studies	10	18	26	28	30	33	32	28	18
MCI *APOE*-ε4+	I^2 (%)	0.0	0.0	17.8	16.9	0.0	43.9	37.1	0.0	0.0
	No. of studies	7	15	25	25	32	32	32	26	11

SCI = subjective cognitive impairment. MCI = mild cognitive impairment. *APOE*=apolipoprotein E.
I^2 statistics were obtained from random-effects meta-analyses in data aggregated across studies in 5-year age groups according to cognitive status and *APOE*-ε4 carrier status. An I^2 statistic value greater than 50% was considered significant heterogeneity between studies (*).

eTable 8. Prevalence estimates from published vs. unpublished studies

	All	Published	Unpublished	p-value published vs. unpublished
Normal cognition				
Number of studies	40	35	5	
Number of participants	2914	2854	60	
Prevalence	22 (17-27)	22 (18-27)	18 (4-51)	0.69
SCI				
Number of studies	20	17	3	
Number of participants	697	667	30	
Prevalence	24 (16-34)	23 (16-32)	42 (16-77)	0.33
MCI				
Number of studies	47	41	6	
Number of participants	3972	3794	178	
Prevalence	47 (41-53)	48 (43-54)	29 (14-51)	0.06

Data are number or point estimate (95% confidence interval).
SCI = subjective cognitive impairment. MCI = mild cognitive impairment. *APOE*=apolipoprotein E.
The prevalence estimates were generated from generalized estimating equations. Prevalence estimates are displayed at the mean age. Amyloid positivity was modeled using age and cognitive status, published (yes/no) and interactions between the variables and published as predictors.

eMethods

Alzheimer disease-type dementia meta-analysis

Search methods
We ran a web-based query on 11/09/2014: ("Alzheimer disease"[Mesh] OR "dementia"[Mesh] OR "alzheimer" OR "alzheimer's" OR "demented" OR "mental impairment" OR "memory impairment" OR "cognitively impaired" OR "cognitive decline" OR "senile" OR "cognitive impairment" OR "MMSE" OR "Mini-mental state examination" or "Mini mental state examination" OR "CAMDEX" OR "Cambridge Mental Disorders" OR "NINCDS-ADRDA") AND (prevalence[Mesh] OR "prevalence") AND ("1995/01/01"[Date - Publication] : "2014/09/11"[Date - Publication]) AND (English[Language]). In addition, we manually identified articles through checks of bibliographies and citations. Articles were considered as relevant if they reported age-stratified estimates of prevalence, were published after 01/01/1995, were conducted in Europe, were written in English, and were population or community based.

Statistical methodology
Prevalence by age was represented against the midpoint of the age category (e.g. 62.5 for 60-65 years old). In studies reporting age and sex-stratified prevalence estimates, age-stratified estimates were computed as weighted averages across sex. A random-effects meta-analysis of age-specific prevalence estimates was performed. To verify suitability of this method, variance of each estimate was first computed from reported 95% confidence intervals assuming a normal distribution or from total sample size and size of the population with the disease assuming a binomial distribution. Analyses were done using Stata version 12.0 (StataCorp, College Station, TX, USA). Prevalence estimates were weighed by number of participants in the age group and pooled. A nonlinear curve was fitted based on 8 time points at 5-year age intervals (age 62.5, 67.5, 72.5, 77.5, 82.5, 87.5, 92.5, 97.5) using Graphpad Prism software (San Diego, CA, USA) to create Figure 4a.

Results
The search returned 5,488 articles of which title and abstract were reviewed. Reasons for excluding records based on screening of title and abstract were irrelevant topic, methods or design; non-European based studies; not including participants from the general population or community; and duplicate studies. Full-text articles were assessed for eligibility and reasons for exclusion were irrelevant topic, methods or design; review; reporting prevalence of dementia in general, MCI, or cognitive test results; prevalence not stratified by age group; non-European based studies; not including participants from the general population or community; inclusion of early onset AD cases; and duplicate studies. From these and hand-searches, we identified 10 relevant studies (Supplementary Methods Table). Studies were mostly located in Mediterranean countries, including 4 Spanish studies. All studies reported using the NINCDS-ADRDA criteria for establishing the diagnosis of probable AD, except one that reported the use of DSM-IV. Nine out of ten studies enrolled individuals aged ≥65 years and had a sample size >1,000. Overall prevalence estimates of AD varied between 2.9% and 7.2%. Studies consistently showed an increase in prevalence across ages. Meta-analysis showed that prevalence of AD approximately doubled every five years between 70 and 90 years old and more moderately after that. Predicted pooled prevalence was 0.05 (95% confidence interval [CI], 0.00-2.02) for age group 60-65 years old, 0.37 (95% CI, 0.00-2.34) at 65-70 years old, 1.66 (95% CI, 0.00-3.64) at 70-75 years old, 4.1 (95% CI, 2.11-6.09) at 75-80 years old, 7.92 (95% CI, 5.90-9.94) at 80-85 years old, 13.34 (95% CI, 11.27-15.40) at 85-90 years old, 20.57 (95% CI, 18.44-22.70) at 90-95 years old; and 29.85 (95% CI, 27.64-32.08) at ≥95 years old.

Individuals involved in literature search and support: Gayan Perera, Myriam Alexander, Kristen Bibeau, Lisa Ford, Lianna Ishihara, Nadia Foskett, Gerald Novak and Mark Gordon

Lifetime risks for Alzheimer disease-type dementia

We adapted published data on lifetime risks from Genin et al.[62] in order to compare the *APOE* genotype-specific amyloid positivity estimates with *APOE* genotype-specific lifetime risks for AD-type dementia. Lifetime risk estimates for AD-type dementia were averaged across men and women. A nonlinear curve was fitted based on 3 time points at 10-year age intervals (age 65, 75, 85) to create Figure 4b.

Supplementary Methods Table

* Age inclusion criteria. NR=not reported.

					Prevalence by age group (years) in % (95% confidence interval or proportion)									
Reference	**Period**	**Age ***	**No.**	**Overall prevalence**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**85-89**	**90-94**	**95+**
Andersen, 1997[63]	1993-1994	65-84	3,299	4.7 (156/3299)	NR	NR	NR	1.4 (16/1118)	3.2 (30/948)	7.5 (55/733)	11.0 (55/500)	NR	NR	NR
Benedetti, 2002[64]	1996	≥75	238	6.7 (3.7-11.1)	NR	NR	NR	NR	NR	1.3 (1/79)	6.2 (5/81)	8.9 (4/45)	29.4 (5/17)	
Gascon-Bayarri, 2007[65]	2001	≥70	1,754	7.2 (127/1754)	NR	NR		NR	1.5 (11/749)	3.9 (19/492)	11.8 (33/280)	21.2 (32/151)	39 (32/82)	
Gavrila, 2009[66]	2003-2005	65-96	1,500	2.9 (2.1-4.2)	NR	NR	NR	0.3 (1/333)	1.4 (4/286)	4.1 (8/195)	6.3 (7/111)	11.4 (10/88)		
Ott, 1995[67]	1990-1993	≥55	7,528	4.5 (339/7528)	NR	0.2 (4/2613)		0.9 (24/2563)		7.4 (121/1643)		26.8 (190/709)		
Prencipe, 1996[68]	1992	≥65	968	5.2 (3.8-6.6)	NR	NR	NR	1.3 (7/544)		.9 (32/359)		16.9 (11/65)		
Ravaglia, 2002[69]	1999	≥65	1,016	3.0 (1.9-4.4)	NR	NR	NR	.3 (2/563)		1.51 (5/335)		19.5 (23/118)		
Tognoni, 2005[70]	2000	≥65	1,600	4.2 (68/1600)	NR	NR	NR	0.6 (3/458)	0.9 (4/414)	3.5 (13/371)	8 (12/150)	15.8 (23/145)	20.9 (13/62)	
Tola-Arribas, 2013[71]	2009	≥65	2,170	5.5 (4.5-6.5)	NR	NR	NR	0.7 (4/549)	1.3 (6/475)	6.0 (27/449)	9.9 (36/364)	16.9 (37/219)	28.9 (33/114)	
Virues-Ortega, 2011[72]	1987-2003	≥75	546	5.6 (3.7-7.5)	NR	NR	NR	NR	NR	2.8 (6/216)	5.4 (9/165)	9.3 (11/118)	19.1 (9/47)	

ADNI protocol

Part of the data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5- year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

German Dementia Competence Network (DCN) information

The German Dementia Competence Network (DCN) was launched in 2002 by 14 academic centers of excellence in Germany, and was funded by the German Federal Ministry for Education and Research (BMBF) by €25 million over 5 years. The primary goals of DCN are:

1.) to establish procedures for standardized multicenter acquisition of clinical, biological and imaging data, for centralized data management, and for the evaluation of new treatments
2.) to investigate the genetic contribution to different dementias and its effect on phenotypes and course of disease (PI: Wolfgang Maier)
3.) to test whether magnetic resonance imaging (MRI), and/or CSF- and blood-based biological markers, as well as clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD) over three years. Specifically, sensitive and specific markers of very early AD progression should be developed and evaluated (PI: Johannes Kornhuber).
4.) to test whether a combination therapy between AChE inhibitor and memantine is clinically meaningful in early Alzheimer's disease. Specifically, 2 clinical trials were conducted with patients suffering from MCI and mild to moderate Alzheimer's Disease (AD). These trials have evaluated the efficacy and safety of galantamine and memantine in combination versus galantamine alone (AD) or placebo (MCI) (PI: Isabella Heuser, Lutz Frölich).

The Executive Head of the DCN is Wolfgang Maier, MD, University of Bonn, Germany, the DCN governing board consists of eight PI's from academic institutions. The DCN achieved to recruit over 2000 subjects across Germany, with cognitive impairment of various degree and etiology. To date this cohort, aged 55 to 90 at start, was followed-up by three yearly assessments, a follow-up of 10 years is currently ongoing. A biomaterial, imaging and clinical data bank is in place and is managed for data mining.

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