

Unbiased estimates of CSF beta amyloid 1-42 cut-off in a large memory clinic population

Daniela Bertens, MD; Betty M. Tijms, PhD; Philip Scheltens MD, PhD; Charlotte E. Teunissen PhD; Pieter Jelle Visser MD, PhD.

Supplementary tables and figures

Supplementary Table 1. Distribution of diagnosis per year of CSF collection

| Year | Subjective complaints | MCI | Probable AD | Dementia other |
|------|-----------------------|-------------|--------------|----------------|
| 2001 | 4 (11.76%) | 12 (35.29%) | 11 (32.35%) | 7 (20.59%) |
| 2002 | 8 (13.33%) | 17 (28.33%) | 26 (43.33%) | 9 (15%) |
| 2003 | 11 (13.10%) | 24 (28.57%) | 37 (44.05%) | 12 (14.29%) |
| 2004 | 17 (20%) | 18 (21.18%) | 30 (35.29%) | 20 (23.53%) |
| 2005 | 10 (10.42%) | 20 (20.83%) | 39 (40.63%) | 27 (28.13%) |
| 2006 | 20 (13.70%) | 32 (21.92%) | 62 (42.47%) | 32 (21.92%) |
| 2007 | 38 (20.77%) | 26 (14.21%) | 83 (45.36%) | 36 (19.67%) |
| 2008 | 37 (17.79%) | 40 (19.23%) | 95 (45.67%) | 36 (17.31%) |
| 2009 | 50 (19.46%) | 51 (19.84%) | 100 (38.91%) | 56 (21.79%) |
| 2010 | 38 (20%) | 35 (18.42%) | 79 (41.58%) | 38 (20%) |
| 2011 | 68 (25.56%) | 58 (21.80%) | 98 (36.84%) | 42 (15.79%) |
| 2012 | 37 (14.98%) | 51 (20.65%) | 101 (40.89%) | 58 (23.48%) |
| 2013 | 50 (19.08%) | 54 (20.61%) | 112 (42.75%) | 46 (17.56%) |
| 2014 | 40 (19.23%) | 31 (14.90%) | 88 (42.31%) | 49 (23.56%) |
| 2015 | 19 (14.84%) | 21 (16.41%) | 66 (51.56%) | 22 (17.19%) |

Supplementary Table 2. Baseline characteristics according to time of CSF collection

| 2001-2007 | All (n=654) | SCD (n=104) | MCI (n=137) | AD-type dementia (n=277) | Non-AD type dementia (n=136) |
|--------------------------------|--------------|-------------|-------------|--------------------------|------------------------------|
| Age (years) | 68.3 (8.0) | 64.8 (7.5) | 70.1 (7.4) | 68.9 (8.1) | 68 (7.8) |
| Females (%) | 360 (55%) | 64 (62%) | 82 (60%) | 133 (48%) | 81 (60%) |
| Years of education | 4.8 (1.4) | 5.3 (1.4) | 4.8 (1.4) | 4.7 (1.4) | 4.6 (1.5) |
| MMSE score | 23.7 (5.2) | 28.4 (1.8) | 26.5 (2.7) | 21.1 (4.9) | 22.8 (5.8) |
| APOE-ε4 allele carriers, n (%) | 308 (47%) | 36 (35%) | 59 (43%) | 174 (63%) | 39 (29%) |
| CSF aβ 1-42 (pg/ml) | 592 (257) | 796 (237) | 581 (251) | 463 (169) | 711 (274) |
| CSF tau (pg/ml) | 563(397) | 327 (236) | 546 (398) | 728 (418) | 429 (295) |
| CSF ptau (pg/ml) | 74 (39) | 52 (23) | 75 (40) | 92 (39) | 55.15 (27) |
| 2008-2015 | All (n=1766) | SCD (n=339) | MCI (n=341) | AD-type dementia (n=739) | Non-AD type dementia (n=347) |
| Age (years) | 66.3 (6.5) | 64.2 (5.8) | 67.4 (6.5) | 66.8 (6.6) | 66.5 (6.3) |
| Females (%) | 1029 (58%) | 211 (62%) | 222 (65%) | 362 (49%) | 234 (67%) |
| Years of education | 5.0 (1.3) | 5.4 (1.2) | 5.2(1.4) | 4.9 (1.3) | 4.7 (1.4) |
| MMSE score | 23.5 (5.3) | 28.2 (1.7) | 26.6 (2.4) | 20.2 (5.0) | 23.1 (5.0) |
| APOE-ε4 allele carriers, n (%) | 853 (48%) | 120 (35%) | 175 (51%) | 430 (58%) | 128 (37%) |
| CSF aβ 1-42 (pg/ml) | 700 (294) | 942 (280) | 722 (301) | 525 (172) | 815 (273) |
| CSF tau (pg/ml) | 513 (401) | 313 (194) | 456 (265) | 698 (400) | 380 (493) |
| CSF ptau (pg/ml) | 69 (37) | 52 (25) | 67 (33) | 87 (39) | 49 (24) |

Abbreviations: SCD, subjective cognitive decline; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; APOE, Apolipoprotein E; CSF, cerebrospinal fluid; aβ 1-42, amyloid beta 1-42, n.a. not applicable. Data are mean (SD), unless otherwise specified.

Supplementary Table 3. Cut-point according to period of CSF collection

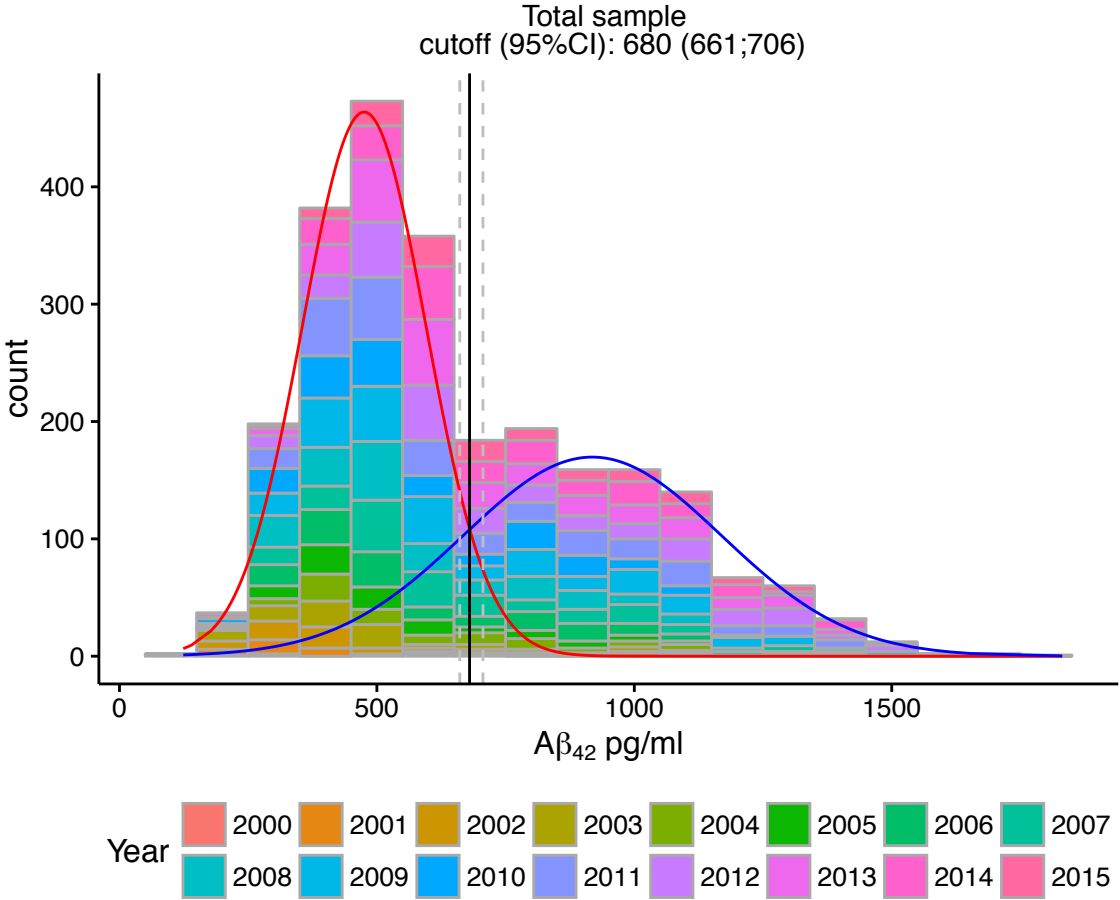
| Year | All (n=2462) | 2001-2007 (n=654) | 2008-2015 (n=1766) |
|------------------------|----------------------------|----------------------------|--------------------|
| a. All | 680 (661-706) | 615 (573-673) | 697 (675-723)* |
| b. No dementia | 664 (623-712) | 696 (578-863) | 672 (628-731) |
| c. Dementia | 694 (670-723) | 610 (567-657) [§] | 715 (687-743)* |
| d. SCD | 621 (526-821) | 761 (549-1015) | 638 (538-1136) |
| e. MCI | 696 (653-754) | 724 (593-834) | 698 (653-773) |
| f. Age ≤ 66.5 | 645 (618-676) | 644 (567-732) | 666 (661-706) |
| g. Age >66.5 | 723 (691-761) [#] | 651 (584-724) | 737 (702-781) |
| h. APOE-e4 non-carrier | 650 (614-695) | 597 (529-697) | 672 (633-712) |
| i. APOE-e4 carrier | 716 (684-780) | 586 (529-672) [§] | 734 (696-780)* |

* Statistically significantly different between 2001-2007 and 2008-2015 cut-off.

[§] Statistically significantly different between 2001-2007 and All cut-off.

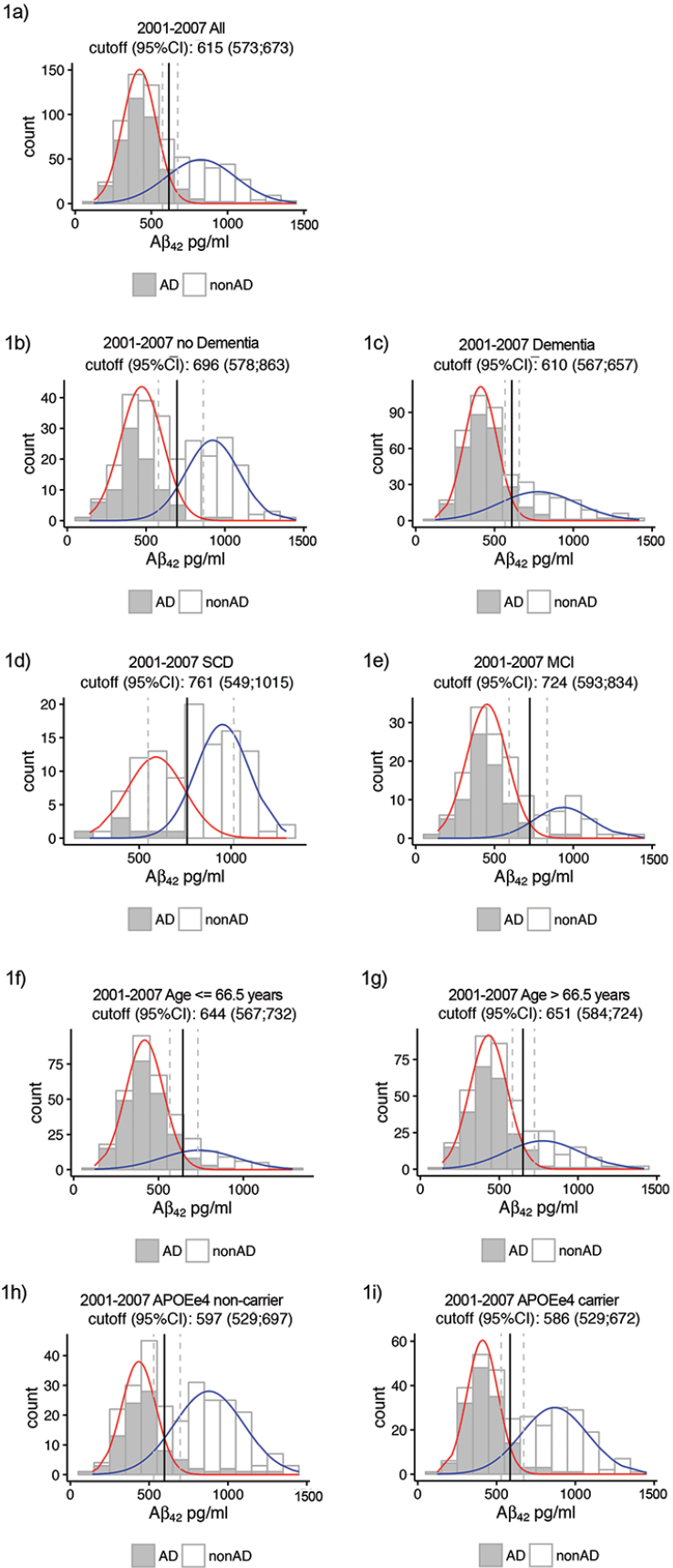
[#] Statistically significantly different from Age <66.5 subgroup.

S-Figure 1: Distribution of CSF Aβ42 values according to year of visit



Colours represent the year that CSF samples were obtained.

S-Figure 2. CSF A β ₄₂ cut-off values based on mixture modeling in 2001-2007 subsample

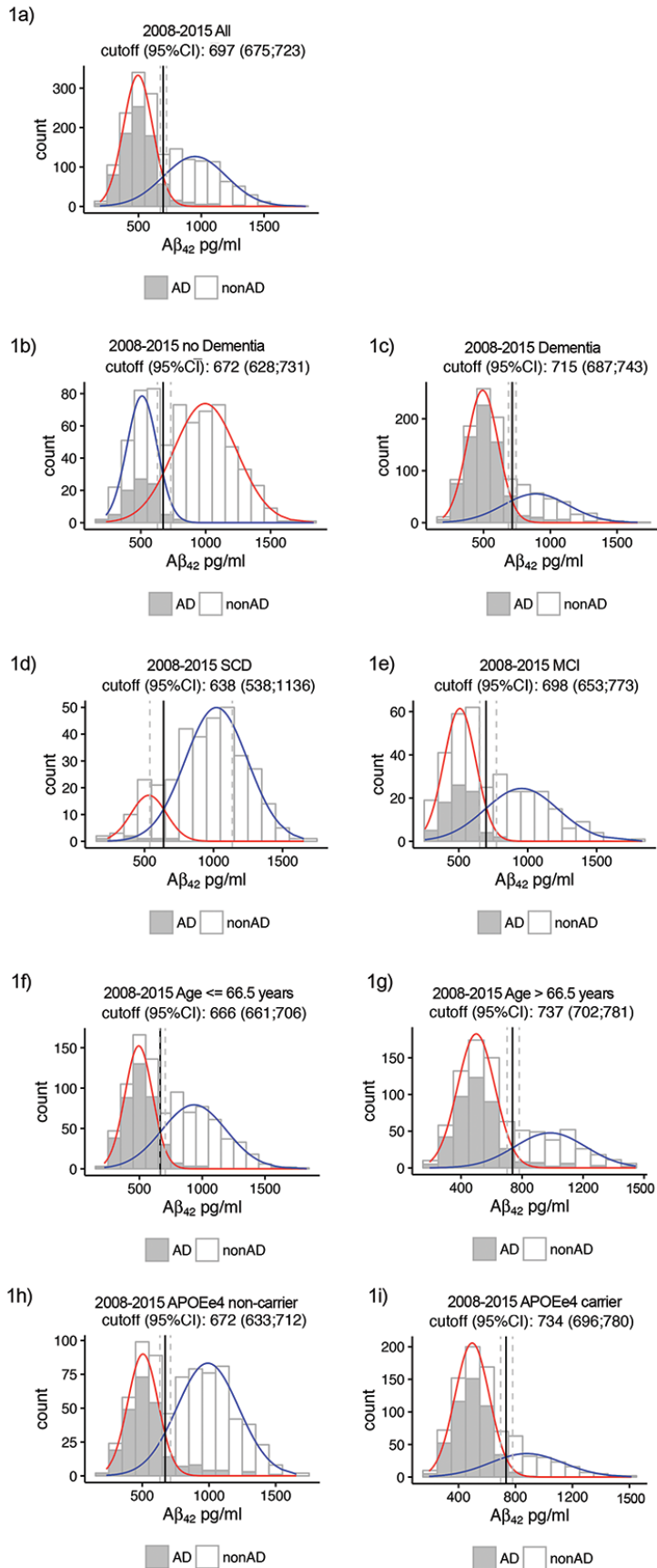


Legend S-Figure 2.

a) Total sample, b) Demented subjects, c) Non demented subjects, d) Subjects with SCD, e) Subjects with MCI, f) Subjects ≤ 66.5 years, g) Subjects > 66.5 years, h) APOE- $\epsilon 4$ allele non-carriers i) APOE- $\epsilon 4$ allele carriers. Subjects with a clinical diagnosis of AD-type dementia at baseline or at follow-up (non-demented subjects) are shown in grey.

Abbreviations: SCD, subjective cognitive decline; MCI, Mild Cognitive Impairment; APOE, Apolipoprotein E; AD, Alzheimer's disease.

S-Figure 3. CSF A β ₄₂ cut-off values based on mixture modeling in 2008-2015 subsample

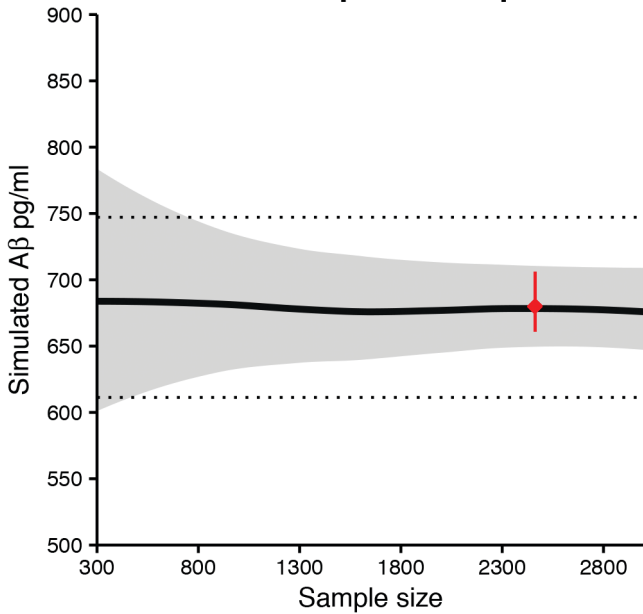


Legend S-Figure 3.

a) Total sample, b) Demented subjects, c) Non demented subjects, d) Subjects with SCD, e) Subjects with MCI, f) Subjects ≤ 66.5 years, g) Subjects > 66.5 years, h) APOE- $\epsilon 4$ allele non-carriers i) APOE- $\epsilon 4$ allele carriers. Subjects with a clinical diagnosis of AD-type dementia at baseline or at follow-up (non-demented subjects) are shown in grey.

Abbreviations: SCD, subjective cognitive decline; MCI, Mild Cognitive Impairment; APOE, Apolipoprotein E; AD, Alzheimer's disease.

S-Figure 4. Effect of sample size on CSF Aβ 42 cut-off and 95% CI



The solid black line represents the mean CSF Aβ 1-42 cut-off per sample size and the grey area represents the 95% CI for that CSF aβ 1-42 cut-off. The dotted lines represent the mean cut-off + or - 10%. The place where the 95% CI crosses the dotted line represents the minimum sample size required (here n=800) to obtain a cut-off of which the 95% CI is within 10% of the mean cut-off. Our data-driven cut-off with 95% CI is represented in red. The modeling was performed in population of which 55% had abnormal CSF aβ 1-42 and 45% normal levels. Abbreviations: aβ 1-42, amyloid beta 1-42.