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Polygenic hazard score in LOAD

Chin Hong Tan, PhD
Department of Radiology and Biomedical Imaging

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Disclosures

- None

Clinical trials

1. Too far advanced into disease
   (Schneider et al., 2014)
   - Solution: Focus on earlier disease stages
     - Low rates of cognitive and clinical decline

2. Absence of AD neuropathology
   (Schneider et al., 2014)
   - Solution: Biomarker positivity for inclusion
     - High screen failure rate

Can we use a polygenic hazard score to identify non-demented individuals at the highest risk of progressing to Alzheimer's dementia?

Outline

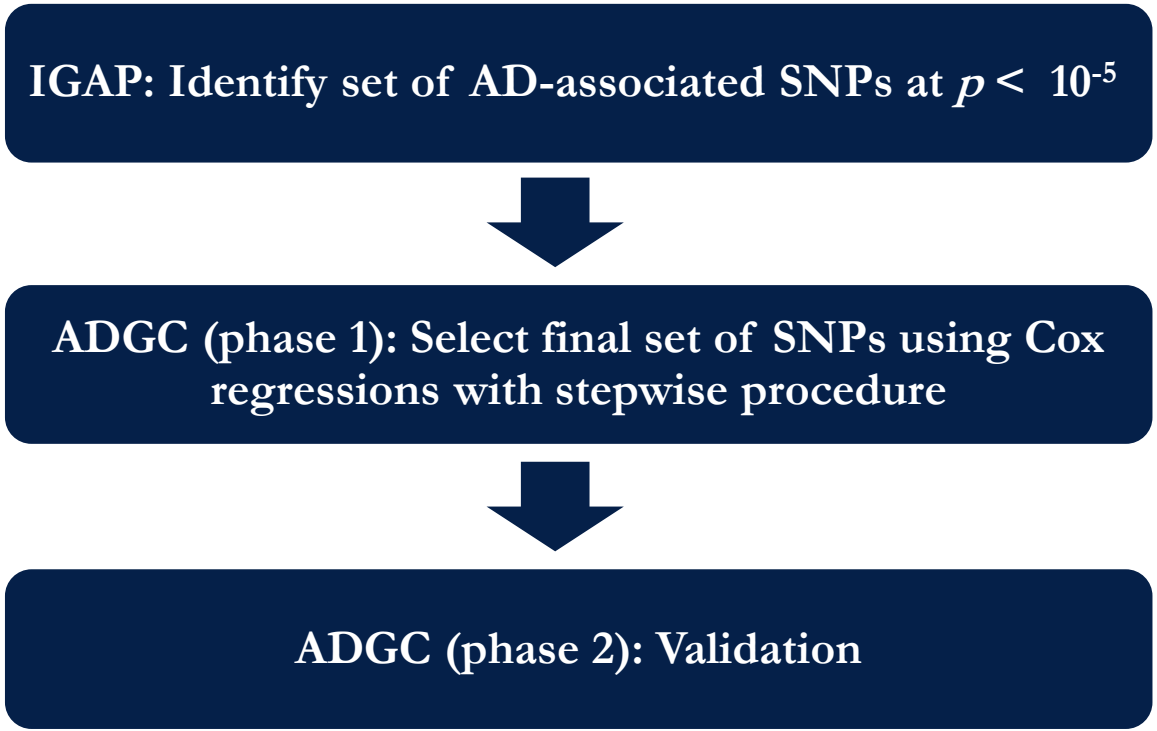
Polygenic hazard score (PHS)

1. Development and validation
   (Desikan et al., 2017; *PLoS Medicine*)
2. Cognitive and clinical decline in preclinical AD and MCI
   (Tan et al., 2017; *Annals of Neurology*)
3. Enrichment marker for CSF/PET amyloid & tau
   (Tan et al., 2018; *Acta Neuropathologica*)

AD polygenic risk

- Apolipoprotein E (*APOE*) ε4
- Other AD-associated SNPs (e.g. Lambert et al., 2013, Desikan et al., 2015)
- PHS: combining 31 AD-associated SNPs in addition to *APOE*
- Polygenic risk score? Polygenic hazard score (PHS)?

Polygenic risk score? Polygenic hazard score?



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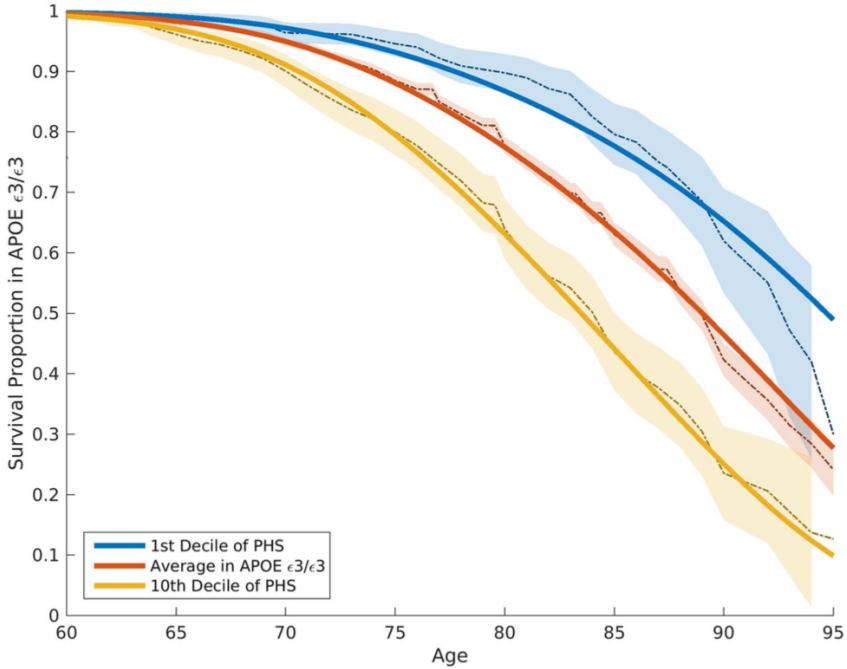
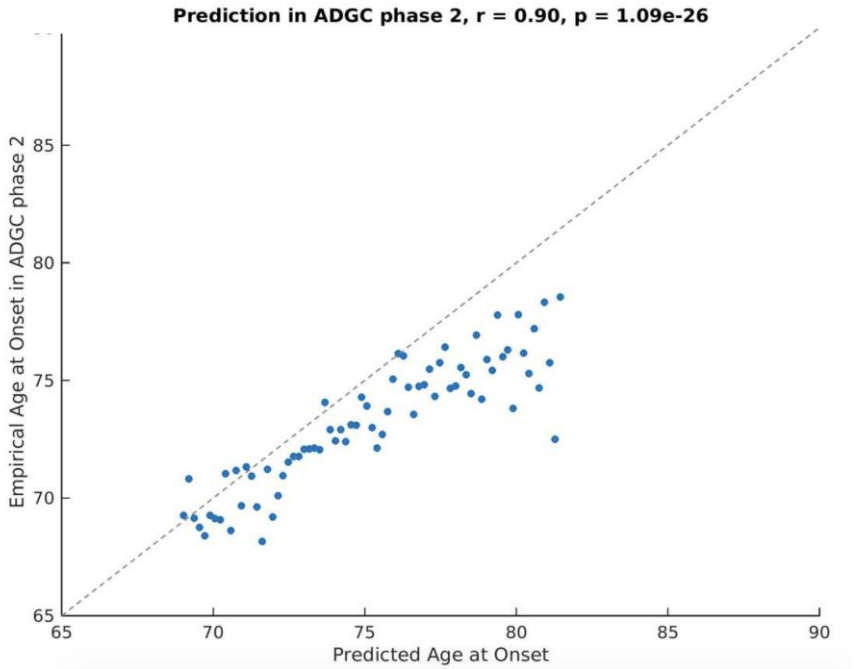
- Polygenic risk score? Polygenic hazard score (PHS)?
- When rather if

PHS – Development and validation





Desikan et al., 2017, *PLoS Medicine*

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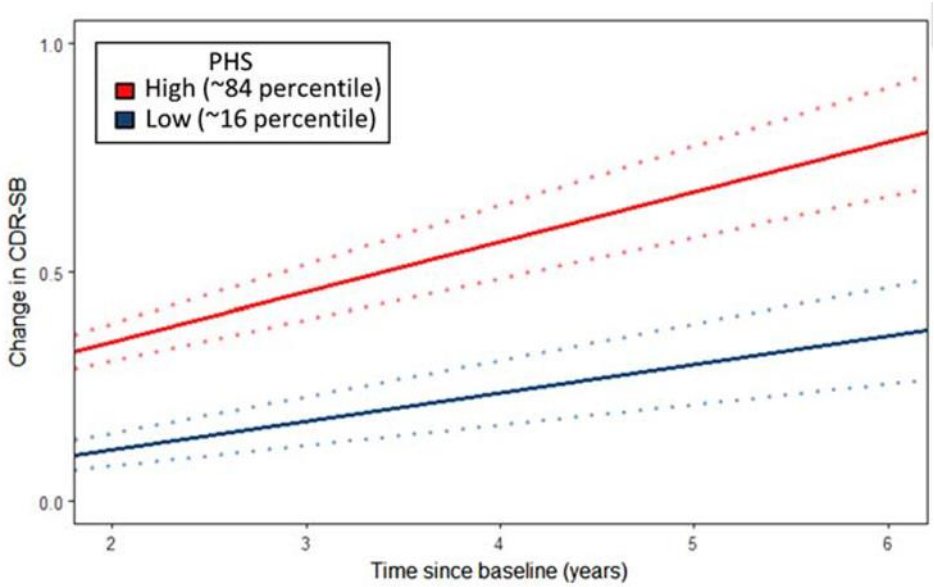
Cognitive & clinical decline

NACC: CN = 1081, MCI = 571

CN & MCI

	PHS*Time		
	ß (SE)	*p*-value	*n*
Logical Memory	**-1·51 (0·68)**	**$2{\cdot}74\times10^{-2}$**	1,224
WAIS-R Digit Symbol	**-1·53 (0·35)**	**$1{\cdot}60\times10^{-5}$**	1,143
Boston Naming Test	**-0·96 (0·24)**	**$6{\cdot}98\times10^{-5}$**	1,239
Trail-Making Test A	**-3·25 (1·00)**	**$1{\cdot}05\times10^{-3}$**	1,255
Trail-Making Test B	**-4·36 (1·04)**	**$2{\cdot}85\times10^{-5}$**	1,212
Digit Span (forward)	**-1·07 (0·39)**	**$5{\cdot}47\times10^{-3}$**	1,258
Digit Span (backward)	-0·59 (0·53)	0·26	1,258

CN: ΔCDR-SB



Tan et al., 2017, *Ann Neurol*

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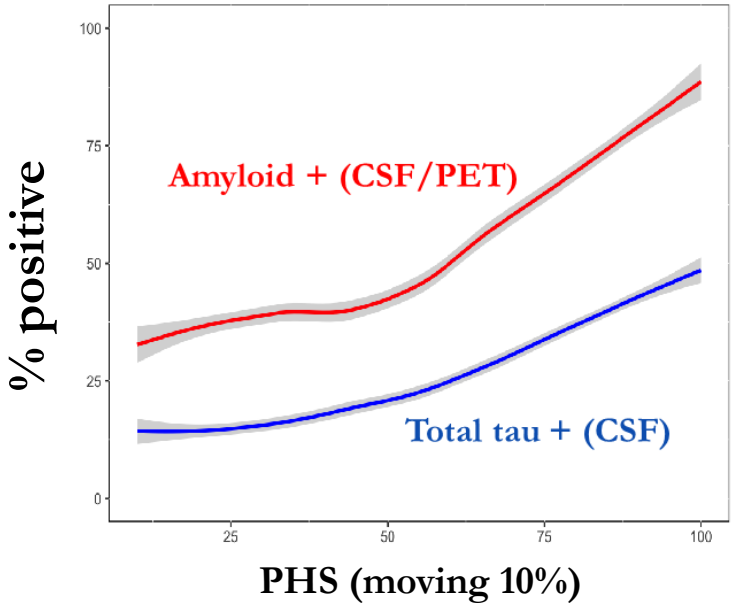
PHS - Predicting biomarker status

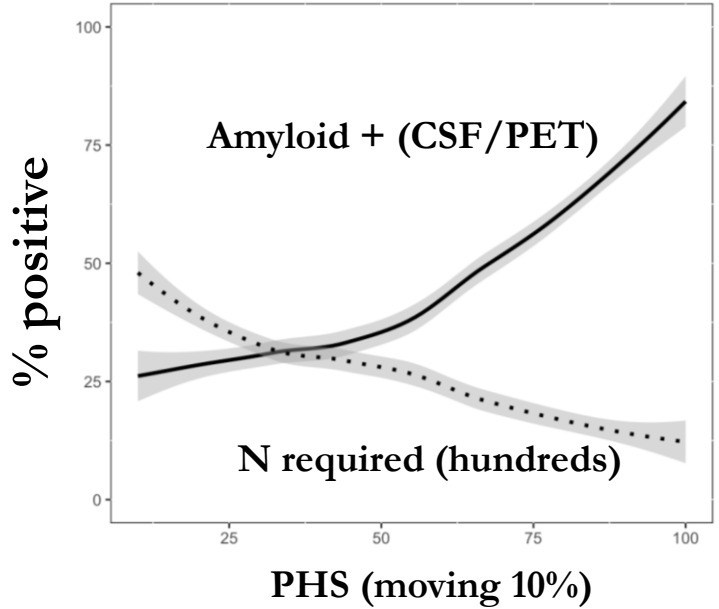
ADNI: CN = 347, MCI = 599

CN + MCI



Tan et al., 2018 *Acta Neuropathol*

CN



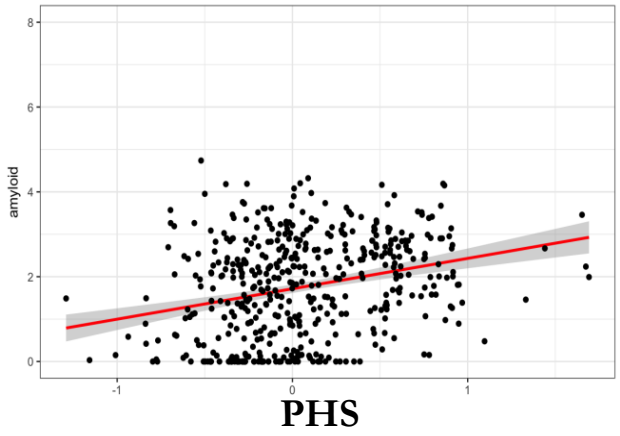
Tan & Desikan, *under review*

PHS - Predicting AD neuropathology

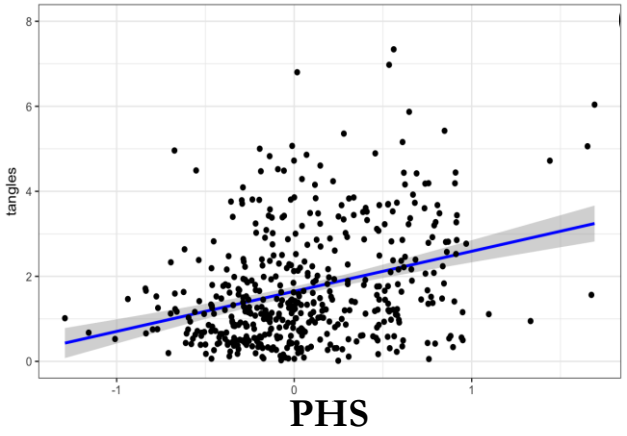
ROSMAP: N = 485

ADNI (CN + MCI)

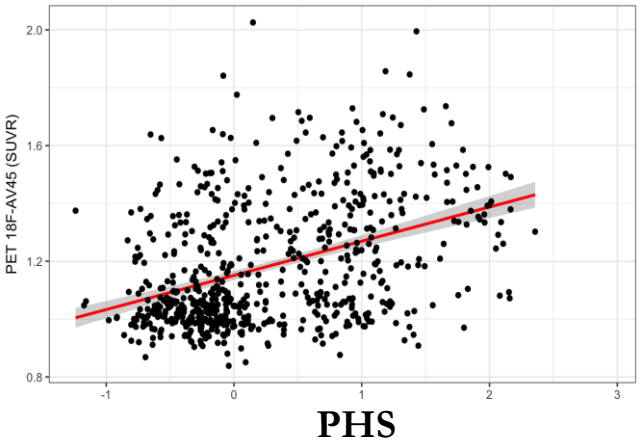
Postmortem amyloid load



Postmortem neurofibrillary tangles



amyloid PET

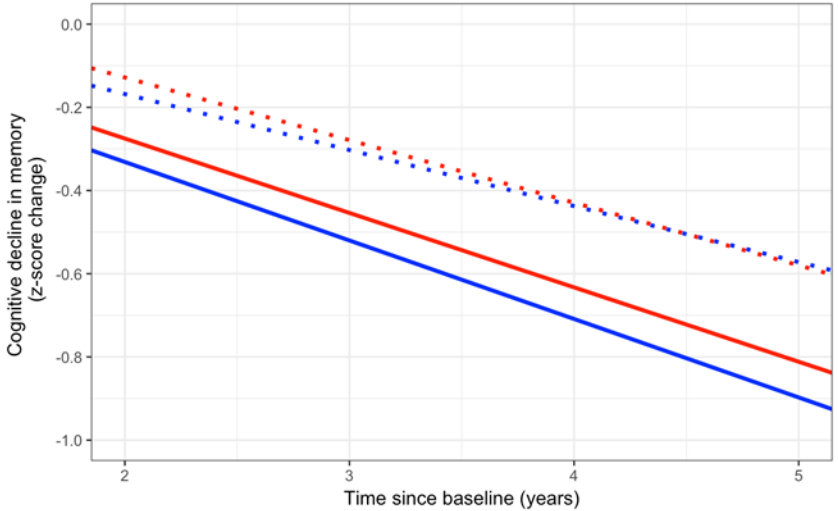


Tan et al., 2018 *Acta Neuropathol*

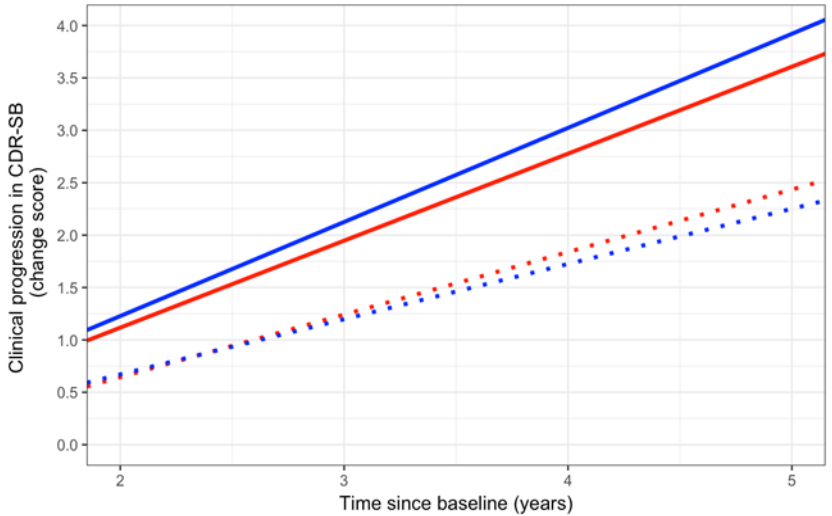
PHS + biomarker: Cognitive and clinical decline

CN + MCI

Memory



CDR-SB



(Biomarker*time) amyloid + / total tau +

high PHS and amyloid + / high PHS and total tau + (PHS*Biomarker*time)

Tan et al., 2018 *Acta Neuropathol*

Conclusion

Can we use a polygenic hazard score to identify non-demented individuals at the highest risk of progressing to Alzheimer's dementia?

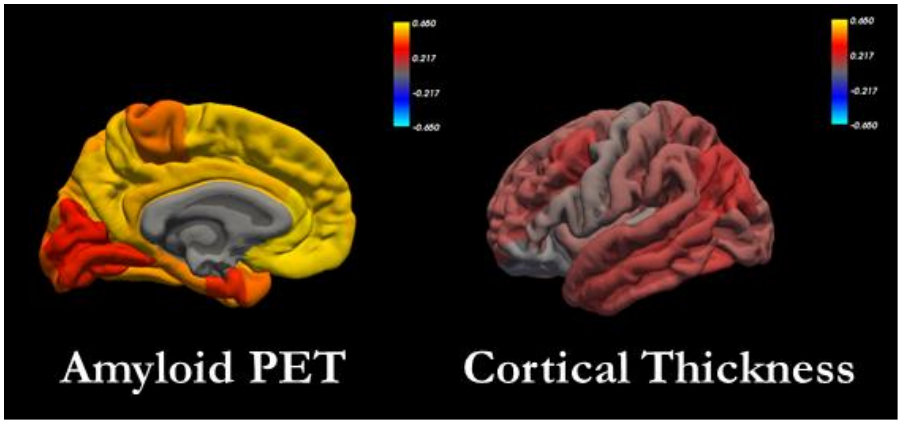
1. Predict biomarker positivity
2. PHS + biomarker : Best predict longitudinal cognitive and clinical decline
3. May be useful in preclinical AD and MCI trials

Ongoing work

1. Multi-dimensional AD prediction score (PHS+MRI+PET etc.)

2. Reanalyzing existing clinical trials data

3. Modifiable non-genetic factors



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