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Polygenic hazard score in preclinical Alzheimer's disease

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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., *under review*)

AD polygenic risk

- Apolipoprotein E (*APOE*) ϵ 4
- Other AD-associated SNPs (small effects)
- PHS: combining *APOE* & 31 AD-associated SNPs
- Polygenic risk score? Polygenic hazard score?
- When rather than if

PHS - Development and validation

IGAP: Identify set of AD-associated SNPs at $p < 10^{-5}$



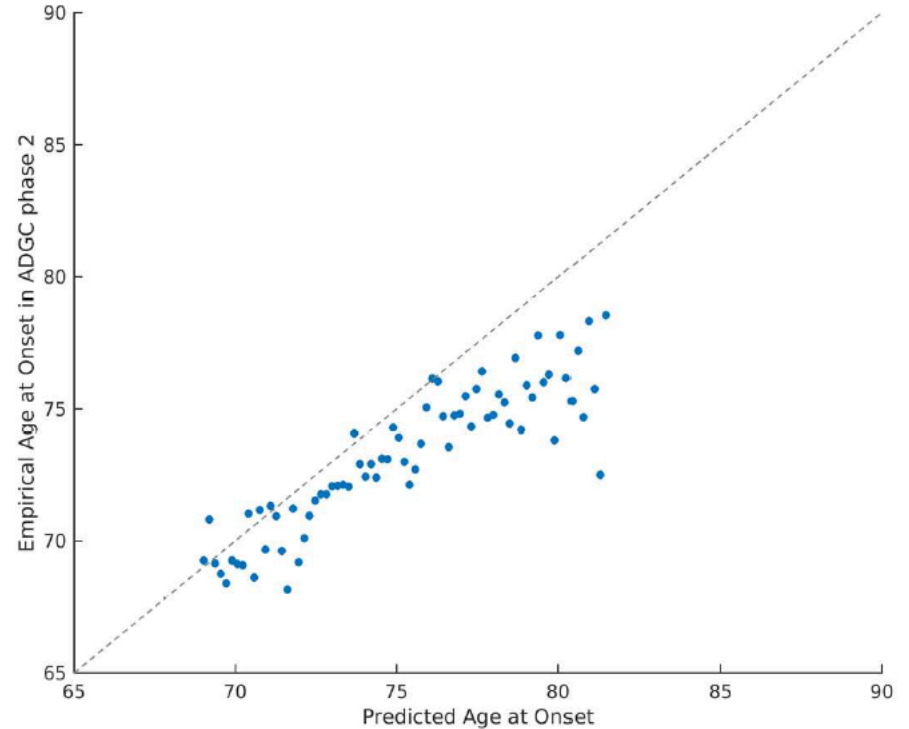
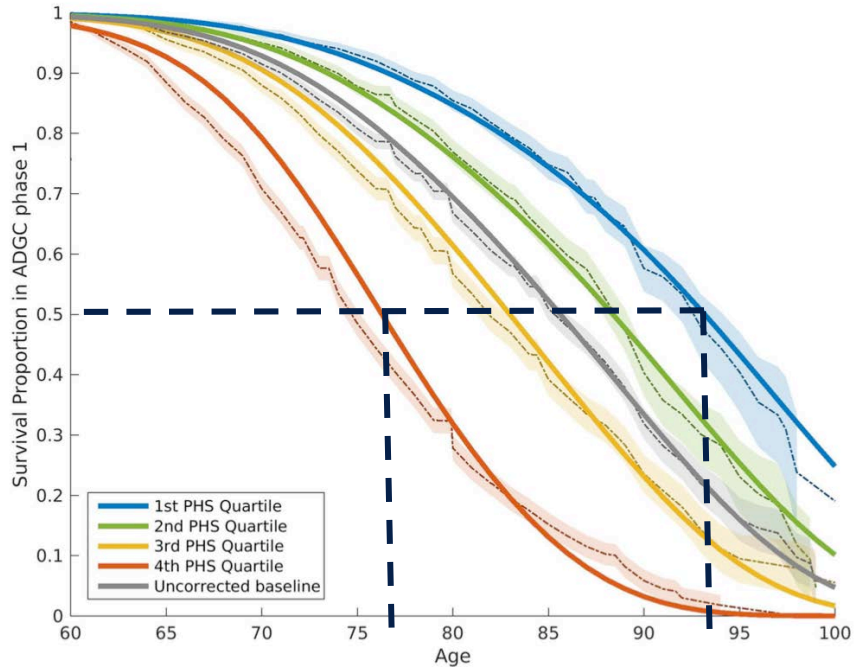
ADGC (phase 1): Select final set of SNPs using Cox regressions with stepwise procedure



ADGC (phase 2): Validation

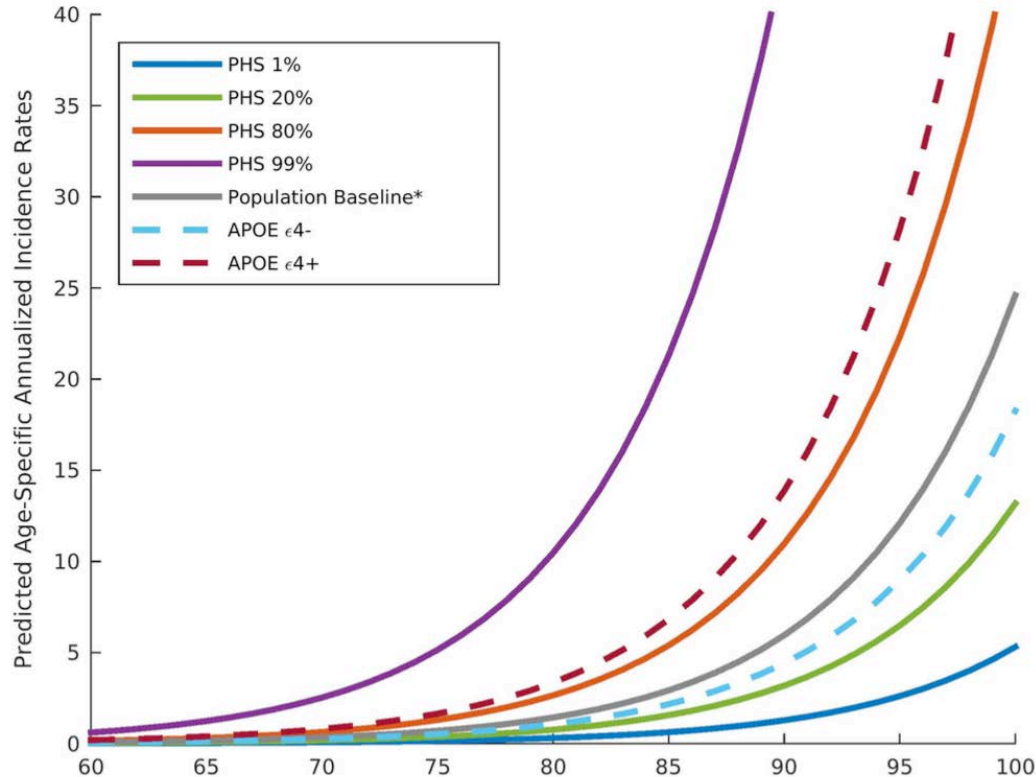
Desikan et al., 2017, *PLoS Medicine*

PHS – Development and validation



Desikan et al., 2017, *PLoS Medicine*

PHS – Annualized incidence rates



- Combining PHS with disease incidence in general US population (Brookmeyer, 1998)
- Instantaneous risk

Desikan et al., 2017, *PLoS Medicine*

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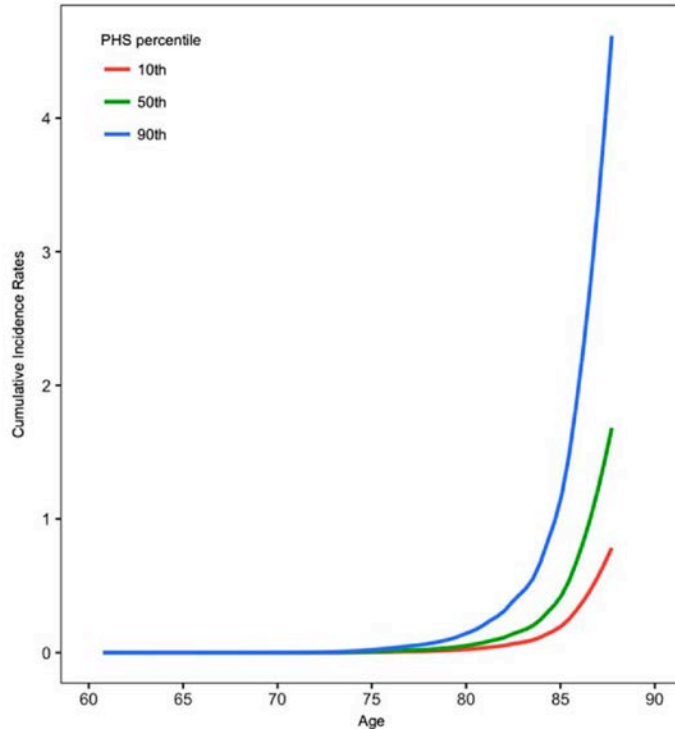
1. Development and validation (Desikan et al., 2017; *PLoS Medicine*)
2. **Cognitive and clinical decline in preclinical AD and MCI** (Tan et al., 2017; *Annals of Neurology*)
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PHS in preclinical AD and MCI

- Clinical trial failures – too advanced in disease
 1. Identifying CN & MCI individuals most likely to progress to AD dementia
 2. Identifying CN & MCI individuals who will experience the greatest rate of cognitive and clinical decline

PHS – Annualized incidence rates

CN

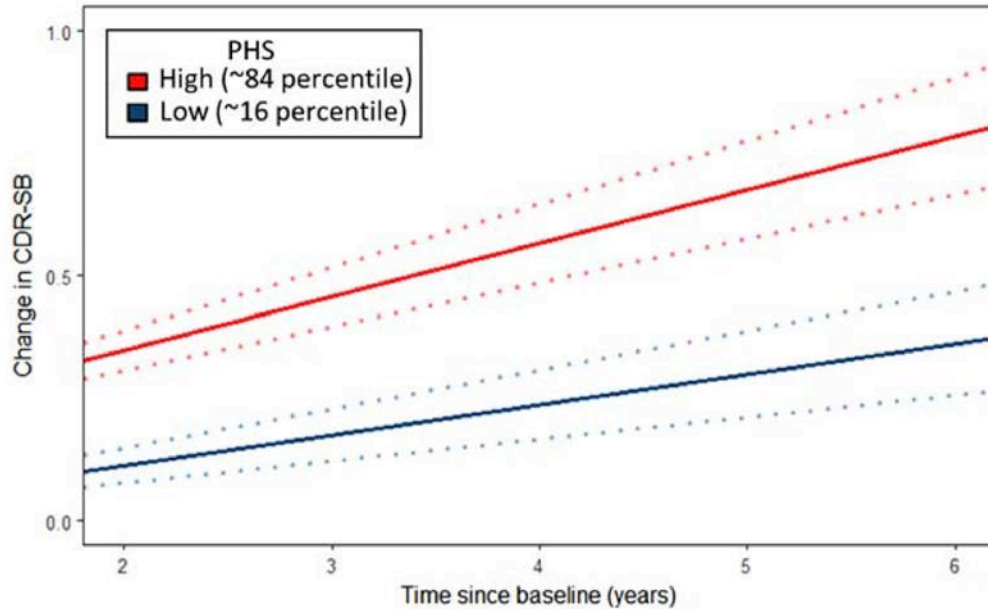


- NACC dataset
- CN = 1081, MCI = 571
- CN: (HR = 2.36, 95% CI = 1.38 – 4.03)
- Using only GWAS between cases and controls to generate polygenic risk may be suboptimal

Tan et al., 2017, *Ann Neurol*

PHS – Clinical decline

CN



- CERAD: mod – freq

1. APOE ($p = 0.61$)
2. PHS in e3e3 ($p < .05$)

Tan et al., 2017, *Ann Neurol*

PHS – Cognitive decline

CN & MCI

	PHS*Time		
	β (SE)	<i>p</i> -value	<i>n</i>
Logical Memory	-1.51 (0.68)	2.74×10^{-2}	1,224
WAIS-R Digit Symbol	-1.53 (0.35)	1.60×10^{-5}	1,143
Boston Naming Test	-0.96 (0.24)	6.98×10^{-5}	1,239
Trail-Making Test A	-3.25 (1.00)	1.05×10^{-3}	1,255
Trail-Making Test B	-4.36 (1.04)	2.85×10^{-5}	1,212
Digit Span (forward)	-1.07 (0.39)	5.47×10^{-3}	1,258
Digit Span (backward)	-0.59 (0.53)	0.26	1,258

- CN individuals
 1. WAIS-R Digit Symbol
 2. Trail-making Test B
 3. Digit Span (forward)

Tan et al., 2017, *Ann Neurol*

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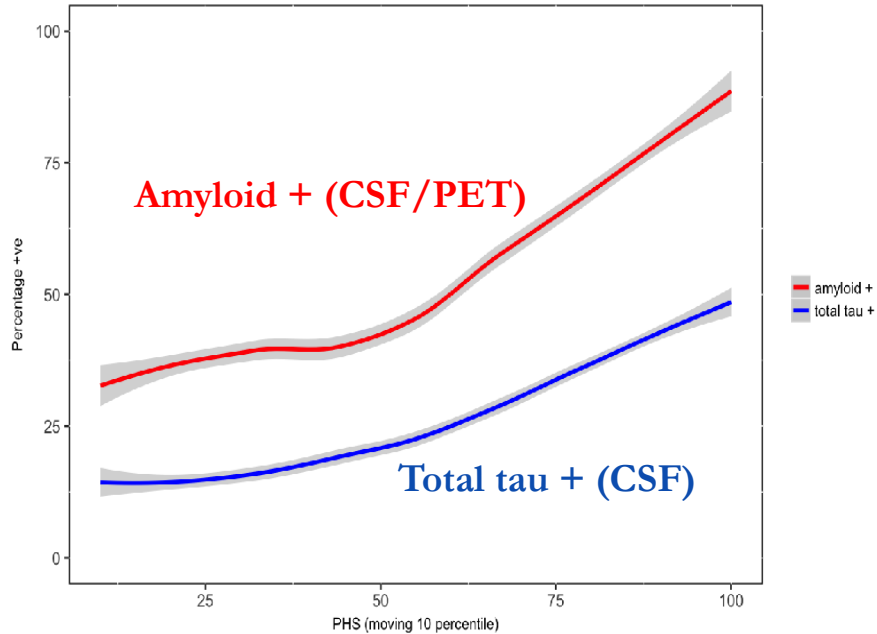
PHS – Enrichment marker for amyloid and tau

- High amyloid PET screen failure rate in preclinical AD
 1. Identifying CN & MCI individuals most likely to be amyloid/tau positive
 2. Combination of PHS and biomarker to predict cognitive and clinical decline.

PHS - Predicting biomarker status

ADNI: CN = 347, MCI = 599

CN + MCI

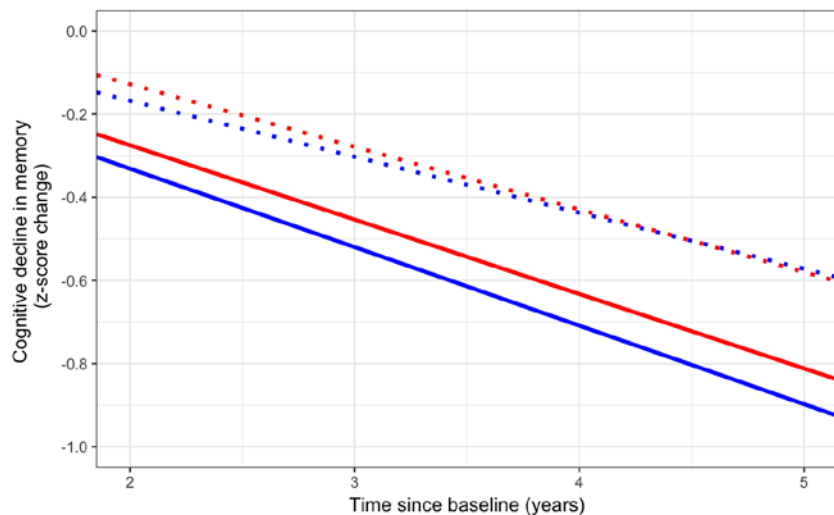


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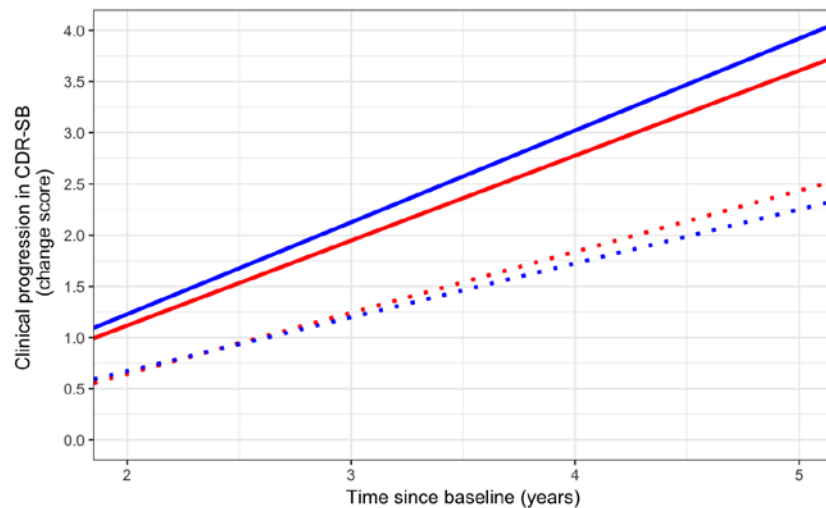
PHS + biomarker: Cognitive and clinical decline

CN + MCI

Memory



CDR-SB



..... amyloid+ — high PHS and amyloid+
..... total tau+ — high PHS and total tau+

Tan et al., *under review*

Conclusion

Polygenic hazard score (PHS)

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

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NACC

ADNI

IGAP

ADGC

ROSMAP

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