

Age Specification Matters? A multi-cohort Evaluation InThe performance of Mid-life Dementia Risk Scores

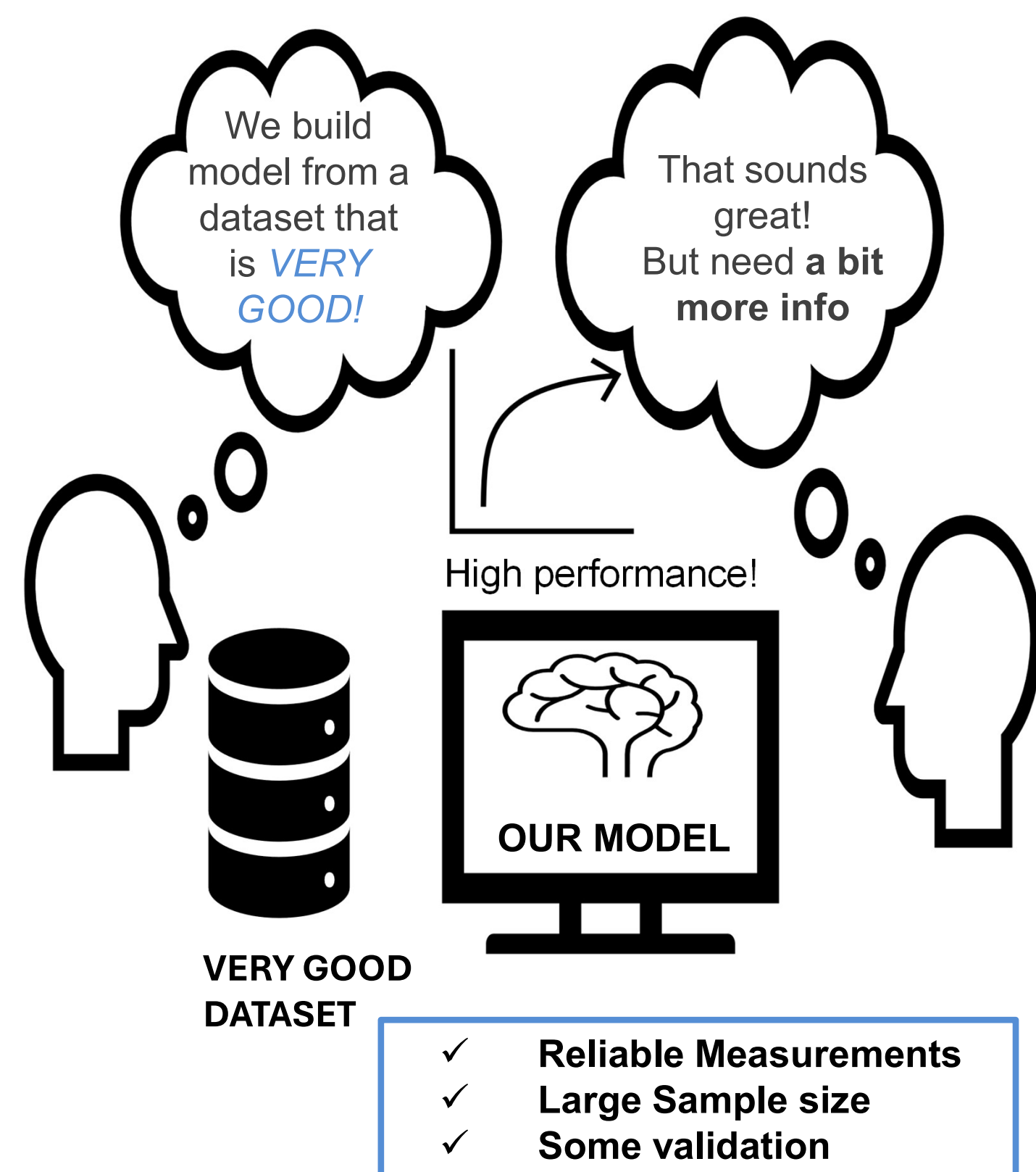
Md Hamidul Huque^{1,2,3*} and Kaarin J. Anstey^{1,2,3}

¹School of Psychology, University of New South Wales, Kensington, NSW, 2033, Australia. ²Neuroscience Research Australia, Randwick, NSW, 2031, Australia. ³UNSW Ageing Futures Institute, University of New South Wales, Kensington, NSW 2033, Australia.

* Corresponding author: MdHamidul.Huque@unsw.edu.au



INTRODUCTION



TO USE THIS MODEL, WE NEED TO KNOW...

- 1) Will it be used in **CLINICAL DIAGNOSIS** or **PREVENTION**?
- 2) How many **RISK FACTORS** are included in the model?
- 3) Are the **RISK FACTORS MODIFIABLE**?
- 4) Does the model include **DISEASE INDICATORS** (or early subclinical markers?)
- 5) What is the **AGE SPECIFICATION**?
 - Linear
 - Categorical
 - Other functional forms?
- 6) What is the **FOLLOW-UP DURATION**? Is it long enough for sufficient exposure and events to occur?

Background: Considerable variability among dementia risk scores in model specification, resulting **heterogeneous predictive performance**^{1,2}. Because **age is the strongest predictor of dementia**, differences in how age is modelled, together with variations in baseline age range and follow-up duration, may substantially influence apparent model discrimination (AUC), independent of the risk factor contribution.

Hypotheses: We hypothesized that

(i) **Continuous age specification** would yield higher AUCs than **categorical age**,

(ii) For categorical age, the **choice of cut off points** for categorical age would influence predictive accuracy.

(iii) **Broader baseline age ranges** combine with **shorter follow up periods** may inflate performance driven mainly by age.

To test these hypotheses,

- we compared the predictive performance of three mid-life dementia risk scores—CogDrisk-ML³, CAIDE⁴, and UKBDRS⁵—using data from three well-established longitudinal cohorts.
- We evaluated model performance with and without age to determine whether differences in discrimination were primarily attributable to age specification rather than differences in the underlying risk factors.

METHODS

1. **Study cohorts-** We aimed to evaluate the performance of CogDrisk-ML tool in predicting MCI using data from the Atherosclerosis Risk in Communities Study (ARIC) study, the Whitehall II study and the UK-Biobank study.
 - The **ARIC cohort** includes 15,792 participants aged 45 to 66 years at their baseline (1987-89) and followed up until wave 7 (2018-19). For this analysis, we included 5,860 participants who were free of dementia at wave 5.
 - The **Whitehall II study** is a longitudinal cohort of 10,308 British civil servants aged 35 to 55 years at baseline, recruited between 1985 and 1988. For consistency with ARIC in terms of age, we included 6,516 participants aged 45 to 64 years.
 - The **Uk-Biobank study** included 287944 individuals aged 50 to 64 years at baseline following exclusion of 608 participants with early onset dementia.
1. **Risk assessment tools:** three midlife risk scores: CogDrisk ML, CAIDE, and UKBDRS were considered. .
2. **Statistical analysis:** Risk prediction was evaluated using Cox proportional hazards models with three age specifications: UKBDRS (continuous), CogDrisk ML (categorical³: 40–49, 50–54, 55–59, 60–64 years), and CAIDE (categorical⁴ age: <47, 47–53, >53 years). Predictive accuracy was assessed using Harrell's C statistics and 95% Confidence interval (CI).

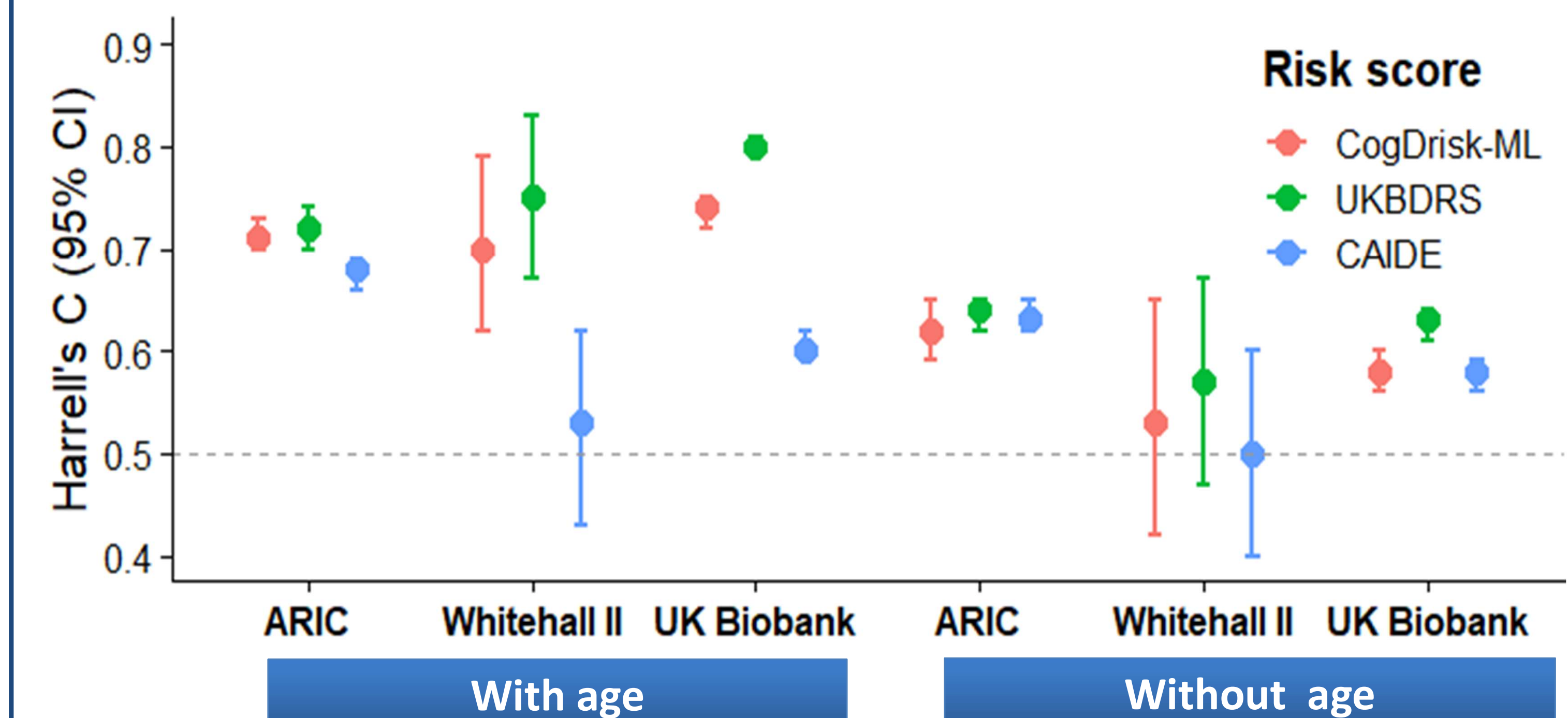
CONCLUSION

- This study is the first to evaluate the impact of age modelling and follow-up duration on dementia risk score performance.
 - Age specification strongly influences dementia risk model performance, with continuous age yielding the highest accuracy, especially with shorter follow-up.
 - UKBDRS outperformed due to age specification, whereas CogDrisk-ML better supports early prevention.
- This findings suggests that caution is needed when comparing risk tools using different age-specification to avoid attributing findings of higher c-statistics to better overall risk assessment of a tool, when instead, variation in performance is only due to age which is not modifiable.

RESULTS

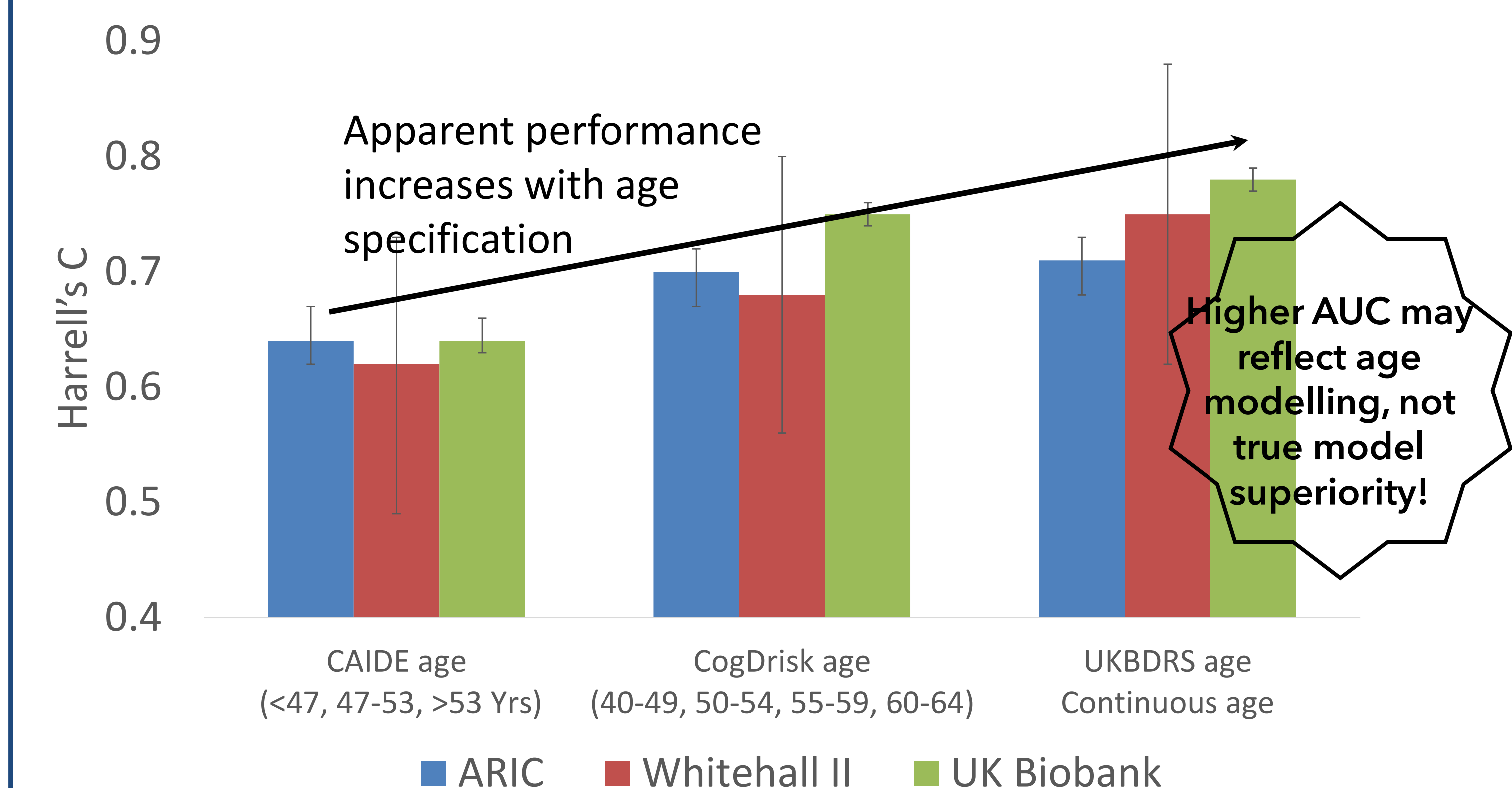
1. Across all cohorts and risk scores, UKBRS provided highest C-statistics, followed by CogDrisk-ML, and CAIDE (Figure 1). Excluding age from the risk scores resulted in similar C-statistics.

Figure 1: Harrell's C (95% CI) for predicting CogDrisk-ML, UKBDRS, and CAIDE risk scores.



2. In age-and-sex only models, continuous age produced the highest Harrell's C-statistics followed by categorical age in CogDrisk-ML and CAIDE (Figure 2).

Figure 2: Age-and-sex-only model



3. The superior performance of the UKBDRS within the UK Biobank sample may be significantly driven by development sample bias .

ACKNOWLEDGEMENTS: KJA is funded Wellcome Trust CARE Grant, which also provides support for HH. Huque is also supported by 2024 Ageing Future Institute (2024). The authors also acknowledge all the studies and respective funding agencies for providing data for the analysis.

REFERENCES: 1. Anstey, K.J., Zheng, L., Peters, R., Kootar, S., Barbera, M., Stephen, R., et al. Dementia risk scores and their role in the implementation of risk reduction guidelines. *Frontiers in Neurology*. 2022;12:2436
2. Huque, M.H., Eramudugolla, R., Li, M., Kiely, K.M., Peters, R., Anstey, K.J. A critical review and classification of dementia risk assessment tools to inform dementia risk reduction. *The Journal of Prevention of Alzheimer's Disease*. 2025;100333.
3. Huque, H., Welberry, H., Eramudugolla, R., et al. Development of a Midlife specific CogDrisk algorithm (CogDrisk-ML) to enable validated implementation of dementia risk assessment from midlife to late-life. *Age and Ageing*. 2025;54(7):
4. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol*. 2006 Sep;5(9):735-41.