



Executive Dysfunction as the Cardinal Cognitive Feature of CADASIL

Processing speed and executive dysfunction lead a genotype-stratified profile; timed measures detect impairment before the global screen. Baseline findings from the United States CADASIL Consortium.

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KEY TAKEAWAY In the largest North American CADASIL cohort to date, cognition is led by **processing speed (SDMT)** and **executive dysfunction (TMT-B)**, concentrated in **high-risk NOTCH3 carriers**. Timed measures separate from mRS o **a full disability stratum earlier than the MoCA**, supporting genotype-based enrichment and timed cognitive endpoints for trials.

-0.53 SDMT — processing speed
Cohen's d · high-risk vs control

-0.48 TMT-B — executive set-shifting
Cohen's d · high-risk vs control

2.53 MoCA visuospatial / executive
OR · most-affected subdomain

0.78 SDMT — AUC (top rank)
Discriminates mRS ≥ 2

BACKGROUND · DISEASE MECHANISM



- ① Focal small-vessel hits**
NOTCH3 GOM deposition; early white-matter hyperintensities & lacunes in frontal-subcortical circuits.
- ② Circuit disconnection**
Disrupted networks impair processing speed & executive set-shifting — caught early by SDMT / TMT-B.
- ③ Diffuse network failure**
Burden spreads to memory, language & orientation — caught late by the global MoCA.

AIMS

- 1 Characterise the cognitive profile and test genotype stratification.
- 2 Relate cognition to functional disability.
- 3 Evaluate how each cognitive domain discriminates between impaired and unimpaired.

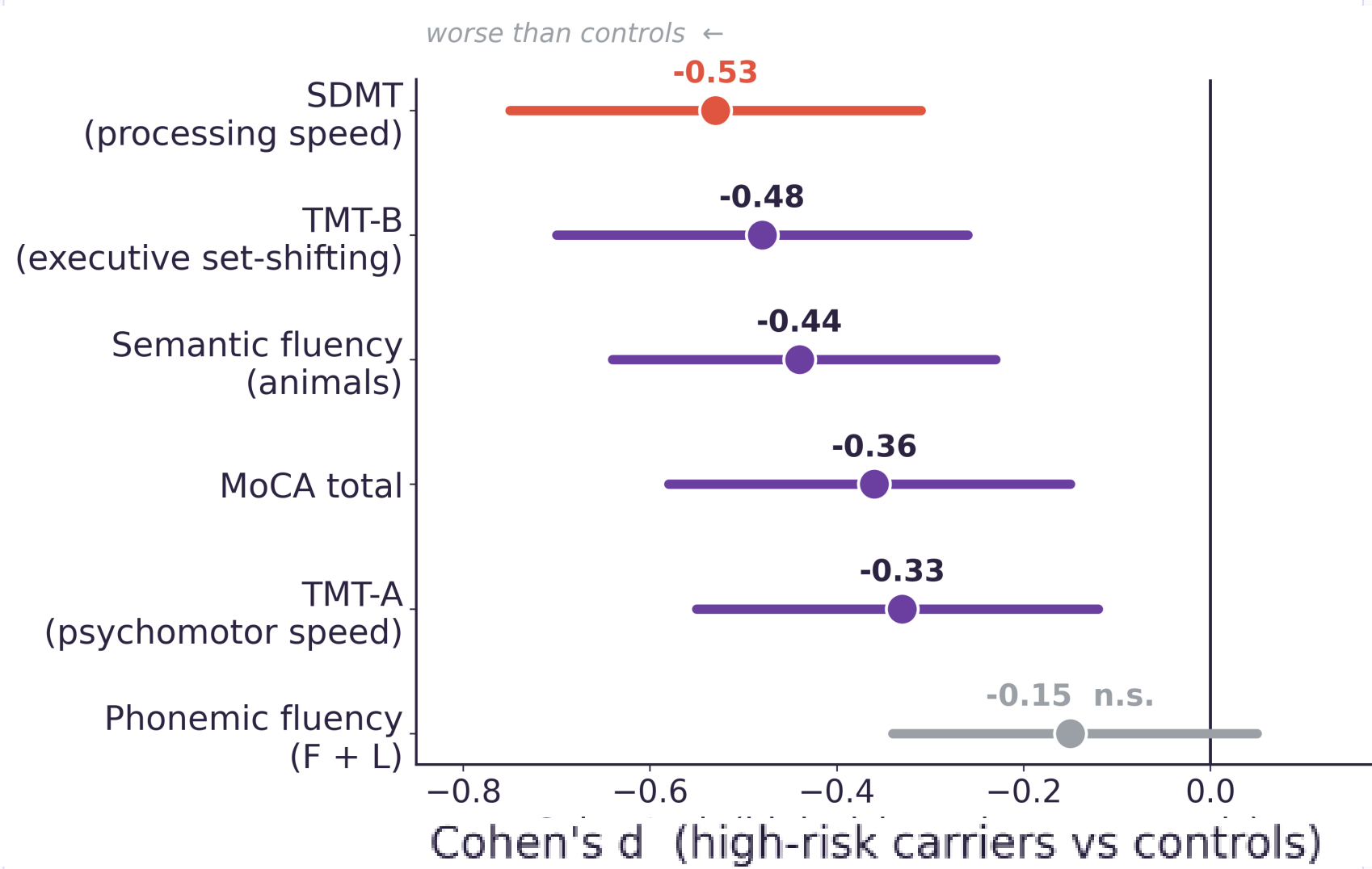
METHODS

- Genotype risk tiers from *NOTCH3* EGFr position (Hack 2023): low 24, med 63, high 256
- Four pre-specified primary outcomes: TMT-B, SDMT (T-scores), MoCA total, phonemic fluency. Bonferroni-corrected threshold $\alpha = 0.0125$ (for the primary outcomes).
- Mixed-effects models with site random intercept; mRS staging, univariable ROC, MoCA-subdomain clustering; TabCAT tablet battery.

COHORT SNAPSHOT

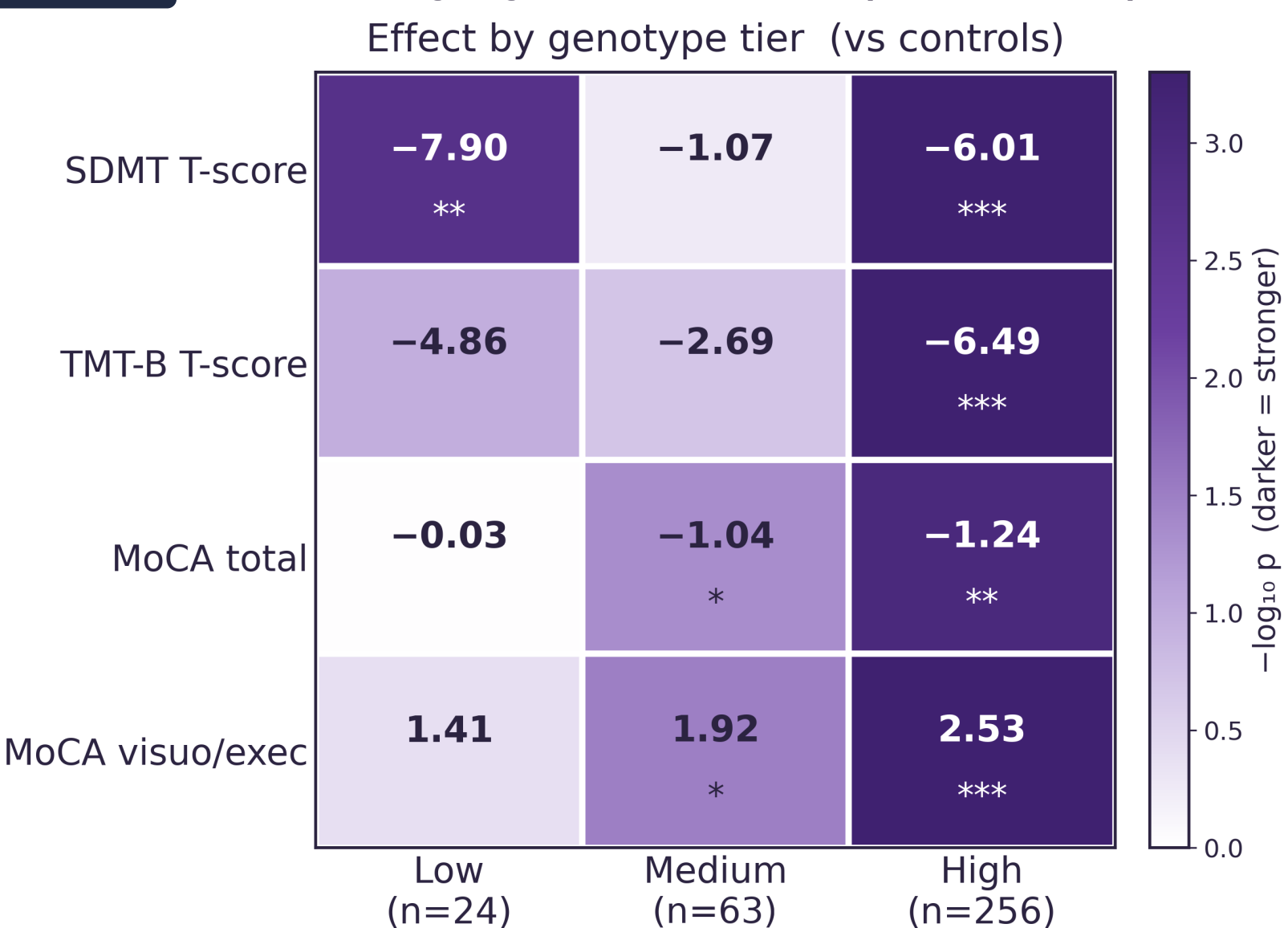
459	116 / 343
ANALYTIC COHORT	CONTROLS / CARRIERS
24 / 63 / 256	~48,
LOW / MED / HIGH	MEAN AGE
63%	44%
FEMALE	MRS 0 · ASYMT.

AIM 1 Domains most affected in CADASIL



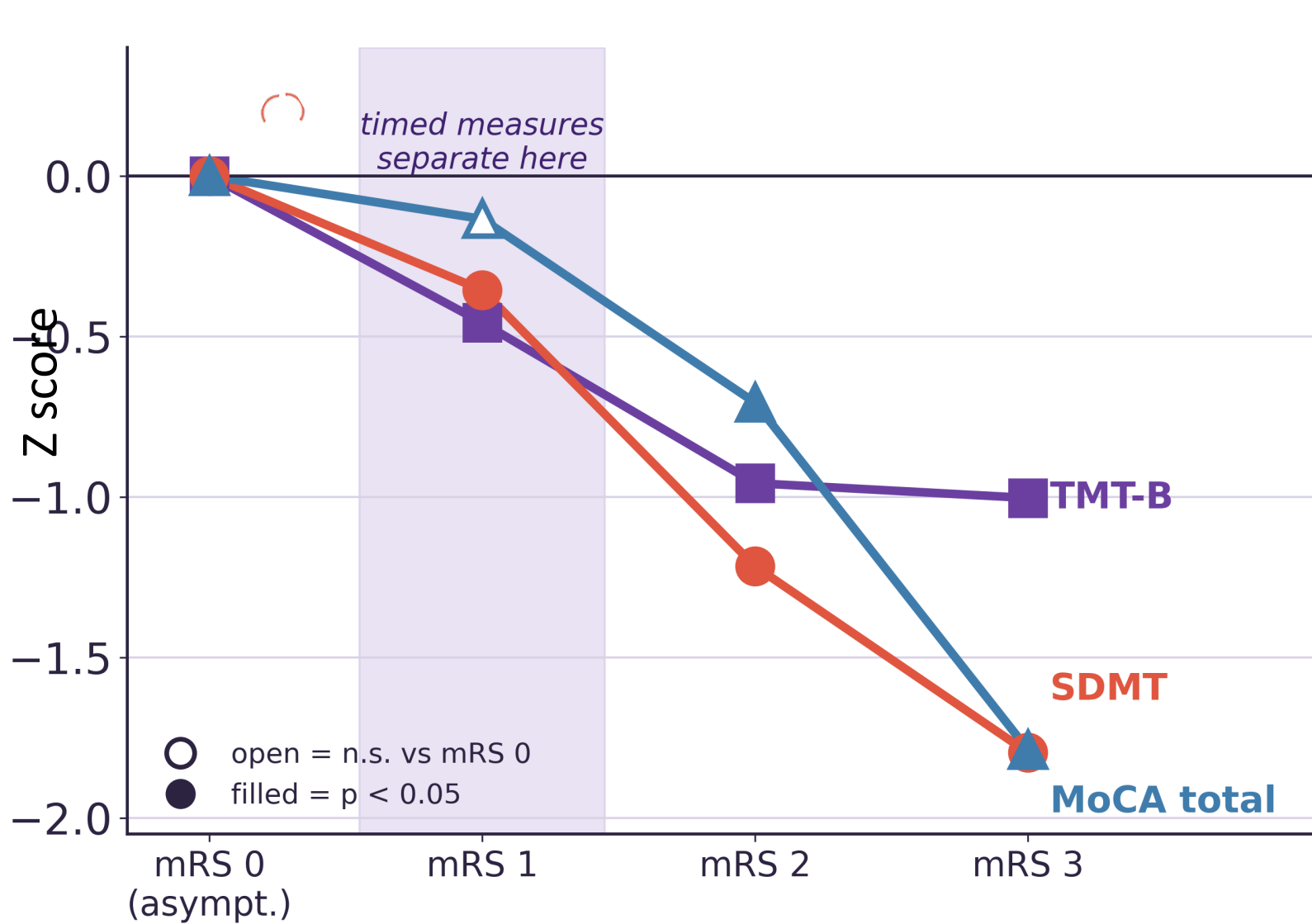
Effect sizes (Cohen's d), high-risk vs controls, across six cognitive measures. All these measures are timed except MOCA.

AIM 1 Disability by Genetic Tier (Hack 2023)



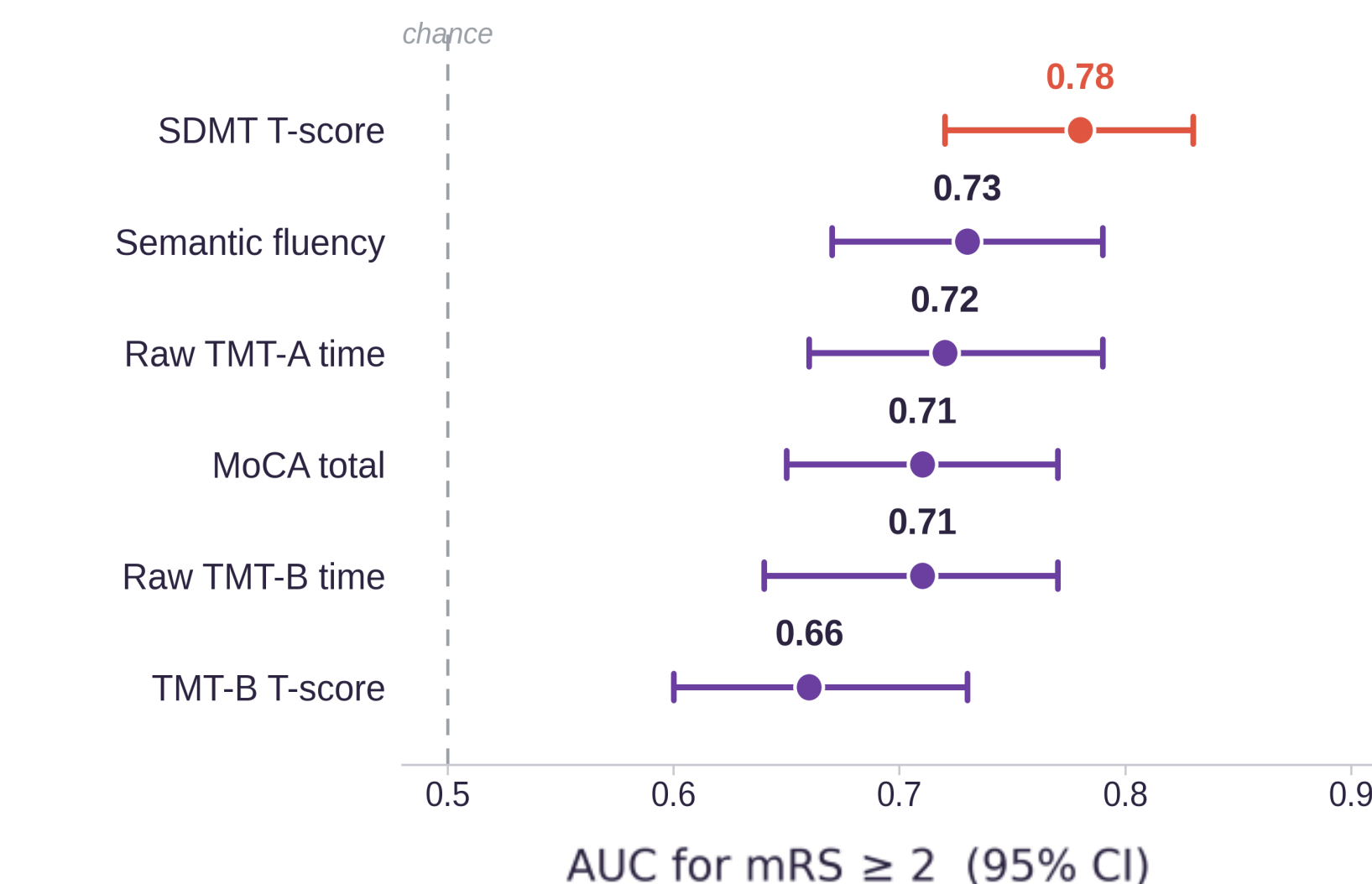
Cells: model-estimated difference from controls (negative = worse); MoCA visuo/exec shown as an odds ratio (>1 = worse). Darker = stronger evidence; *p<.05 **p<.01 ***p<.001. Low-risk SDMT (n=24) imprecise; trend nonlinear.

AIM 2 Timed Measures Separate Before MOCA



Standardized difference from mRS 0 across strata (T-scores ÷ 10, MoCA ÷ sample SD); filled = p<.05; p for trajectory < .001.

AIM 3 Univariable Discrimination of Functional Outcomes



Univariable discrimination of mRS 0,1 vs. 2,3 (AUC, 95% CI). Selected measures, 0.66–0.78; SDMT nominally highest.

AIM 1 · DOMAIN HIERARCHY & GENOTYPE

High-risk carriers show the largest deficits, led by processing speed (SDMT) and executive set-shifting (TMT-B); phonemic fluency is spared. Effects concentrate in the **high-risk tier** rather than forming a smooth gradient.

AIM 2 · WHY IT MATTERS

SDMT and TMT-B are already impaired at **mRS 1** — one stratum before the MoCA total separates at mRS 2. A normal MoCA does **not** exclude early cognitive involvement in CADASIL.

AIM 3 · INTERPRETATION

Timed measures rank among the **strongest discriminators** of disability — but discrimination here is **concurrent, not predictive**. Longitudinal follow-up is required to test temporal ordering.

CONVERGENT & SECONDARY FINDINGS

Impairment rate

Nearly **1 in 5** high-risk carriers fell below the SDMT threshold: 18.0% vs 4.3% of controls (OR 4.83).

Tablet battery

TabCAT Match and Flanker (both $p \leq .005$) reproduce the SDMT and TMT-B profile independently.

Two phenotypes

Clustering yields **preserved** (n = 271) vs **impaired** (n = 68); MoCA <23 reproduces it at 96.5% accuracy.

Asymptomatic

In mRS 0 carriers, cognition is largely intact — with an early executive/visuospatial signal confined to the high-risk tier.

Fluency split

Semantic fluency is impaired (d = -0.44) while phonemic is spared — a pointer for imaging–cognition analysis.

CONCLUSIONS

- Timed measures (SDMT, TMT-B) detect impairment **a full disability stratum before the global screen** and rank among the strongest discriminators of disability.
- Findings support **genotype-based enrichment and timed cognitive endpoints** for CADASIL trials; longitudinal follow-up will test these patterns.
- CADASIL cognition is a **frontal-subcortical profile** led by processing speed and executive dysfunction, concentrated in high-risk *NOTCH3* carriers.

LIMITATIONS

Cross-sectional; strata describe disability, not within-person change.
Small low/medium tiers (n = 24, 63) limit intermediate-genotype inference.
ROC analyses univariable and concurrent; SDMT norms non-US.

KEY REFERENCES

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