

VASCOG-2-WSO Criteria to Disentangle Vascular and Non-Vascular Cognitive Impairment Risk and Sex Differences

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KEY MESSAGE

- **Modifiable factors** (late-life physical and cognitive activity, diabetes, hypertension) **distinguished vascular from non-vascular CI.**
- **Risk profiles differ by sex:** Astroglial injury and daytime sleepiness are more prominent in females, whereas gait speed, education, and late-life engagement stand-out in males.
- These easily measurable risk factors along with consideration of sex-specific differences can guide risk stratification and treatment strategies in clinical settings.

BACKGROUND

Cognitive impairment (CI) is multifactorial, involving both neurodegenerative and vascular processes. Vascular Cognitive Impairment and Dementia (VCID), largely driven by cerebral small vessel disease, has historically been underdiagnosed due to lack of standardized criteria. The new VASCOG-2-WSO criteria integrate neuroimaging markers with harmonized cognitive assessment, offering a unique opportunity to disentangle vascular and non-vascular CI and identify risk factors, including sex-specific profiles.

AIMS

To classify cognitive impairment into vascular vs. non-vascular using VASCOG-2-WSO criteria in a population-based setting and identify associated biological and psychosocial factors.

METHODS

Study population. Total of 932 participants aged ≥ 50 with brain MRIs and CI (MCI o dementia) from the *Mayo Clinic Study of Aging*. **Data collected:** Demographics, cognitive tests, physical functioning, vascular and metabolic conditions, lifestyles (e.g., sleep), behavioral symptoms, PIB-PET, plasma biomarkers ($A\beta$ 42/49, pTau-181, NfL, GFAP), APOE genotype.

Table 1. VASCOG-2-WSO criteria (PMIDs: 40955506 & 41364442)

VCID phenotypes	Definition
Unimpaired (no VCID)	Absence of stroke and SVD; Absence of dementia, no cognitive deficits (cognitive performance > -1 SD age group-specific means), no concern from person/informant; Intact independence (ADL & IADL).
At-risk (preclinical)	Presence of SVD or stroke; Absence of dementia, no cognitive deficits (cognitive performance > -1 SD age group-specific means), no concern from person/informant; Intact independence (ADL & IADL).
Mild (prodromal)	Presence of SVD or stroke; Absence of dementia; Modest cognitive deficits ($-1 \leq SD < -2$ age group-specific means); Concern from person or informant; Intact independence (ADL & IADL).
Major (overt)	Presence of SVD or stroke; Dementia or substantial cognitive deficits (≤ -2 SD age group-specific means); Impaired independence.
Mixed VCID	Any phenotype above + Alzheimer's disease biomarkers.

VCID assessment. We operationalized VASCOG-2-WSO to classify CI into vascular negative/positive (VCID-/+), incorporating cerebrovascular disease (CVD; WMHs, infarcts, clinical stroke) and global cognition z-scores.

Statistical analysis. Multinomial logistic regressions adjusted for age and sex to identified risk factors of VCID vs non-vascular CI. Sex-stratified analyses.

Figure 1. Distribution of VASCOG-Defined Cognitive Impairment Subtypes and Participant Characteristics (n=932)

VCID-: CI without CVD (WMH% < 1.3 , no stroke, no infarcts)
PVCID+: CI with CVD at baseline (WMH% ≥ 1.3 , stroke, or infarcts)
IVCID+: Incident CI + CVD at follow-up.

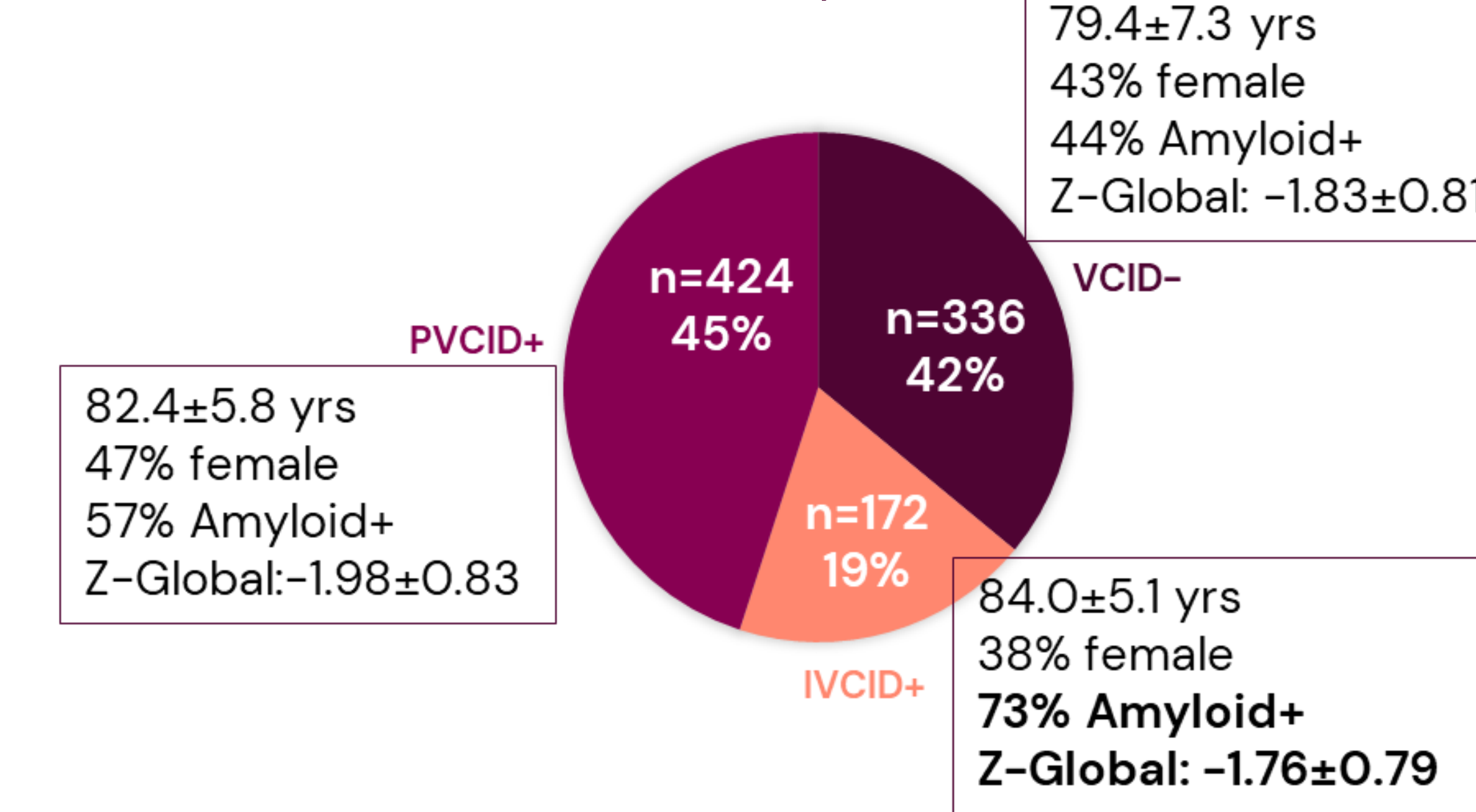
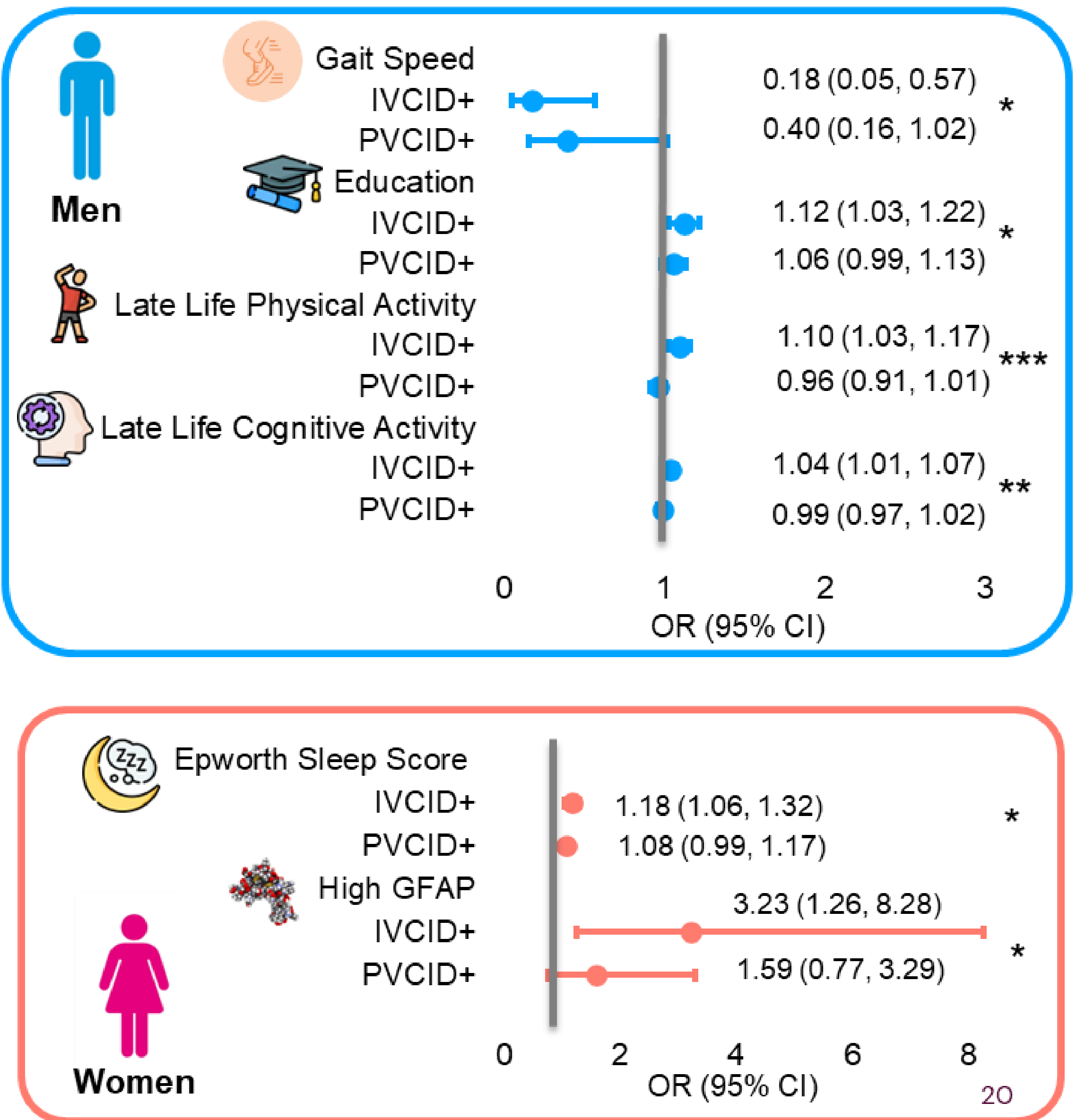


Figure 2. Sex-specific Biological and Psychosocial Factors Associated with VCID Subtypes

Several factors helped distinguish people with IVCID from those VCID-: Education, gait speed, amyloid status, late-life physical and cognitive activity, and cardiometabolic conditions like diabetes and hypertension. These patterns differed between men and women:



Reference group for multinomial logistic regression = VCID negative
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (FDR-adjusted)