



Reduced Alzheimer Neuropathologic Change in Long-duration Type 1 Diabetes: Autopsy Evidence from Joslin Medalists and NACC Participants

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BACKGROUND

Diabetes roughly doubles the risk of dementia, but careful autopsy studies in older adults, overwhelmingly representing type 2 diabetes (T2D), have repeatedly shown that the longstanding association of T2D with increased cognitive decline is driven by cerebrovascular injury (infarcts, small-vessel disease) rather than by additional Alzheimer disease neuropathologic change (ADNC). Whether long-duration type 1 diabetes (T1D) produces the same pathologic substrate has been almost impossible to determine: until recently, few patients with childhood-onset T1D survived to ages at which neurodegenerative pathology accumulates. T1D shares chronic hyperglycemia with T2D but lacks the hyperinsulinemia, insulin resistance, and obesity that usually accompany it. It therefore separates the effects of high glucose itself from those of the wider metabolic syndrome.

The Joslin Medalist Study now provides the opportunity to evaluate autopsy neuropathology of individuals with at least 50 years of T1D. A recent report (Shah et al., 2025) found cognitive impairment and reduced brain volumes on MRI without a corresponding increase in vascular or AD pathology.

Here we expand on this work by directly comparing 33 Joslin Medalists to age- and sex-matched participants from the National Alzheimer's Coordinating Center (NACC) database. We ask whether T1D and T2D produce overlapping or divergent neuropathologic profiles across the major proteinopathies (ADNC, Lewy body disease, LATE-NC/TDP-43) and the full spectrum of cerebrovascular pathology (atherosclerosis, arteriolosclerosis, gross- and micro-infarcts).

THE JOSLIN MEDALIST STUDY

Founded at the Joslin Diabetes Center in 1948, the Medalist program recognizes individuals who have lived with insulin-dependent diabetes for 25, 50, 75, or more years. The Medalist Study has enrolled over 1,000 individuals with at least 50 years of T1D and characterized them with detailed metabolic, renal, cardiovascular, ophthalmologic, and neurologic examination.

METHODS

1:2:3 Matching: each Medalist is matched to two DM+ and three DM- **NACC controls (unimpaired at baseline visit)** on nearest-neighbor age and exact sex, without replacement, resulting in:

Joslin Medalists (T1D duration at least 50 years, n=33).

NACC with diabetes (DM+, n=66) and without (DM-, n=99).

Note: NACC does not distinguish T1D from T2D, but national surveillance shows T2D accounts for about 91% of adult diabetes, so we treat any-DM here as predominantly T2D

Statistics: Inter-cohort differences in each pathology were tested with Fisher's exact tests on a binary high-pathology indicator: high (3-4) vs low (1-2) for A-B-C scores, moderate/severe vs none/low for vascular pathology, and presence vs absence for gross and microinfarcts.

* p<0.05, ** p<0.01

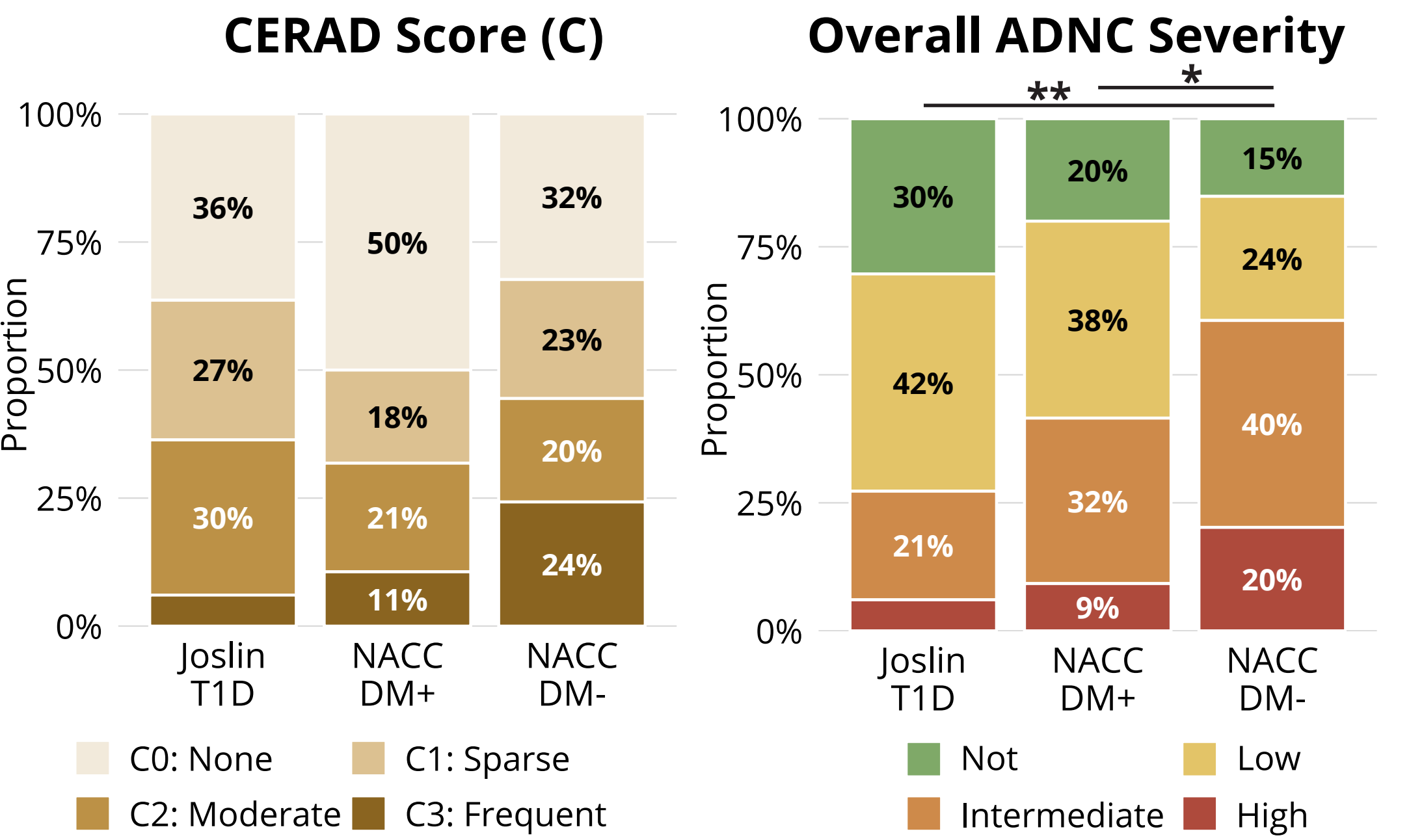
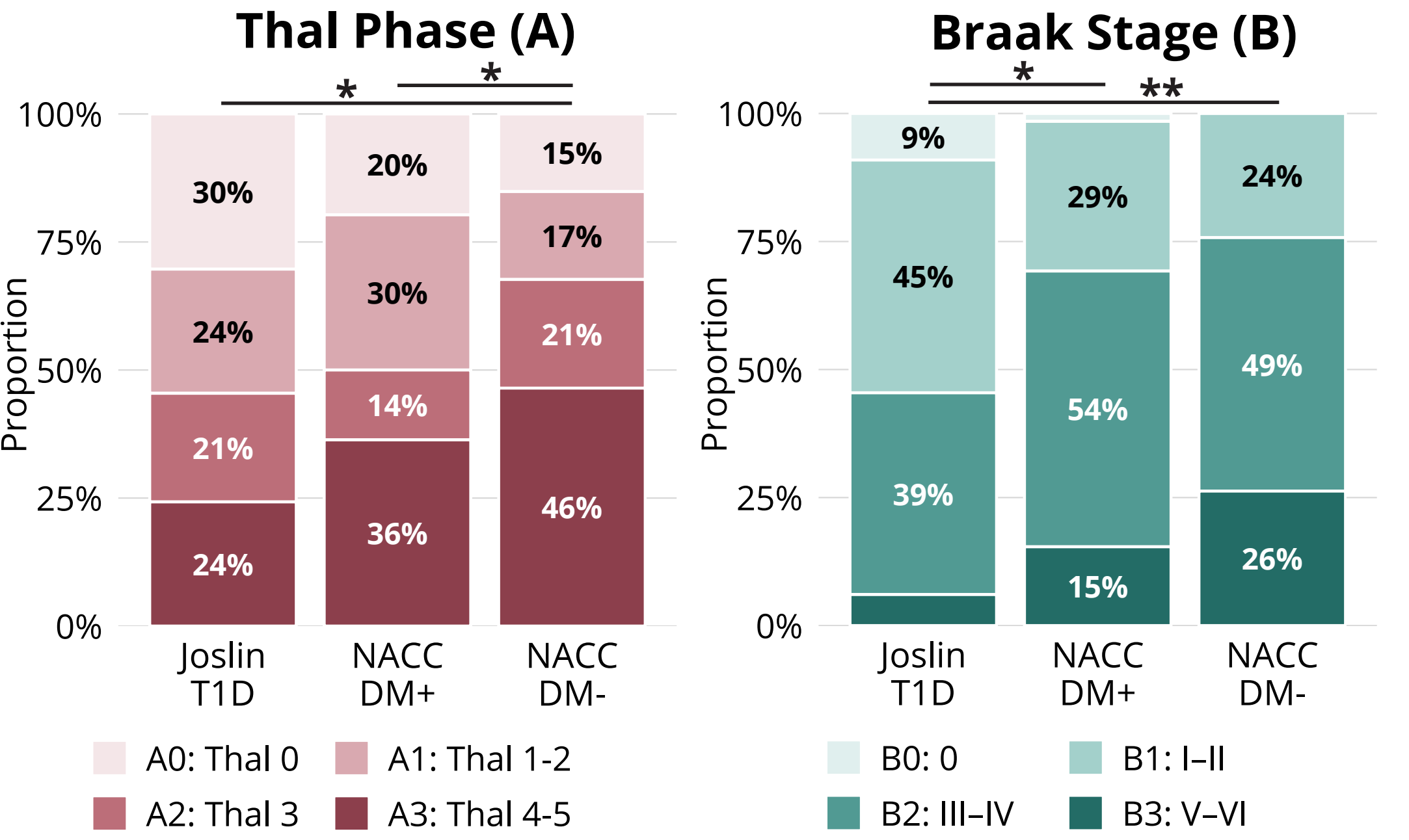


COHORT CHARACTERISTICS

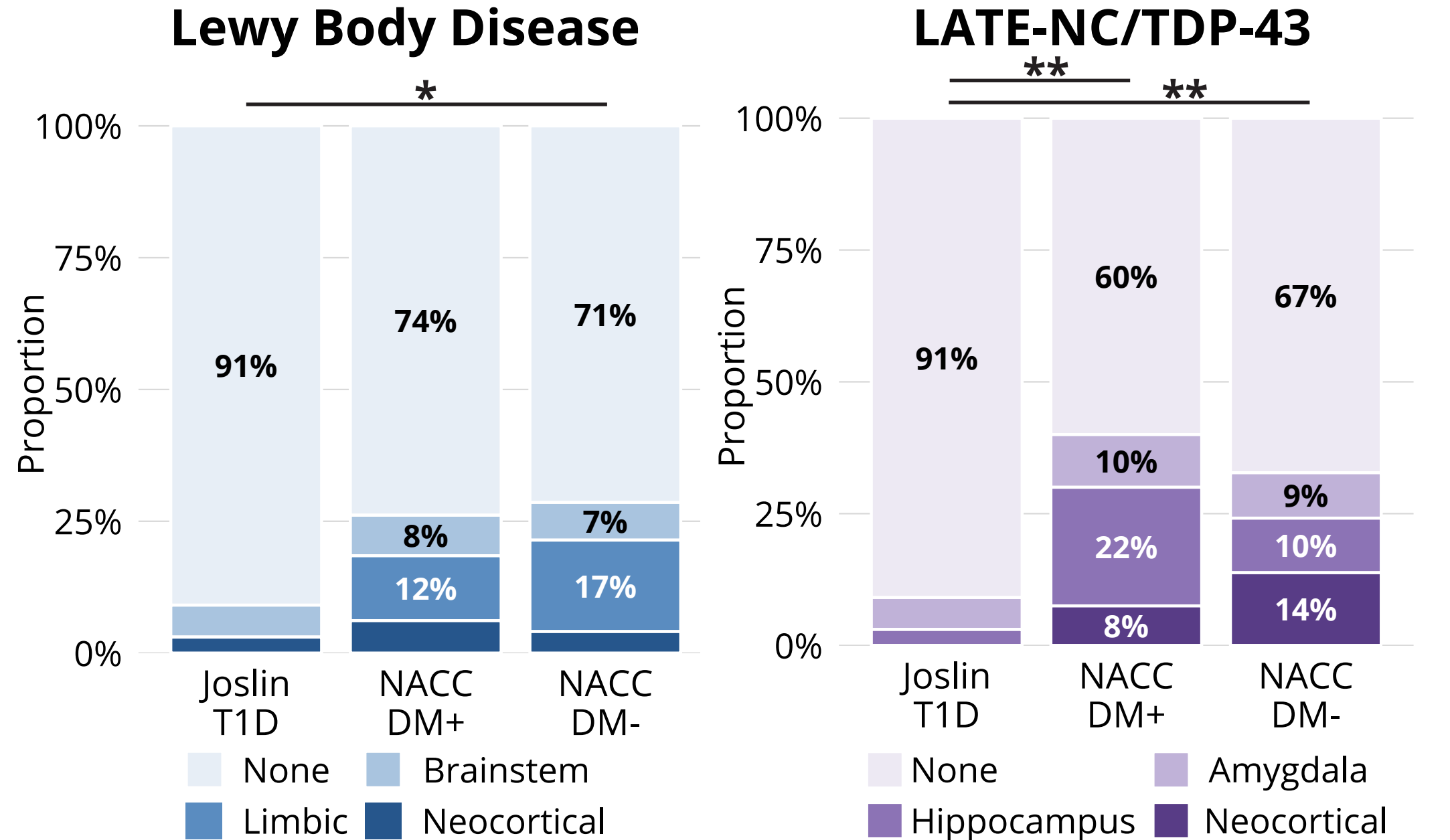
	Joslin T1D	NACC DM+	NACC DM-
N	33	66	99
Age at death, y	82.3 (6.7)	79.7 (6.0)	82.3 (6.6)
Female Sex	10/33 (30%)	20/66 (30%)	30/99 (30%)
BMI, kg/m ²	25.6 (4.1)	29.2 (4.9)	25.8 (4.6)
Systolic BP, mmHg	130.1 (19.2)	134.0 (17.0)	135.0 (16.9)
Ever Smoker	16/30 (53%)	37/66 (56%)	42/98 (43%)
Diabetic Nephropathy	9/33 (27%)		
Diabetic Neuropathy	16/18 (89%)		
Proliferative Retinopathy	15/25 (60%)		

Continuous: mean (SD). Categorical: n (%).

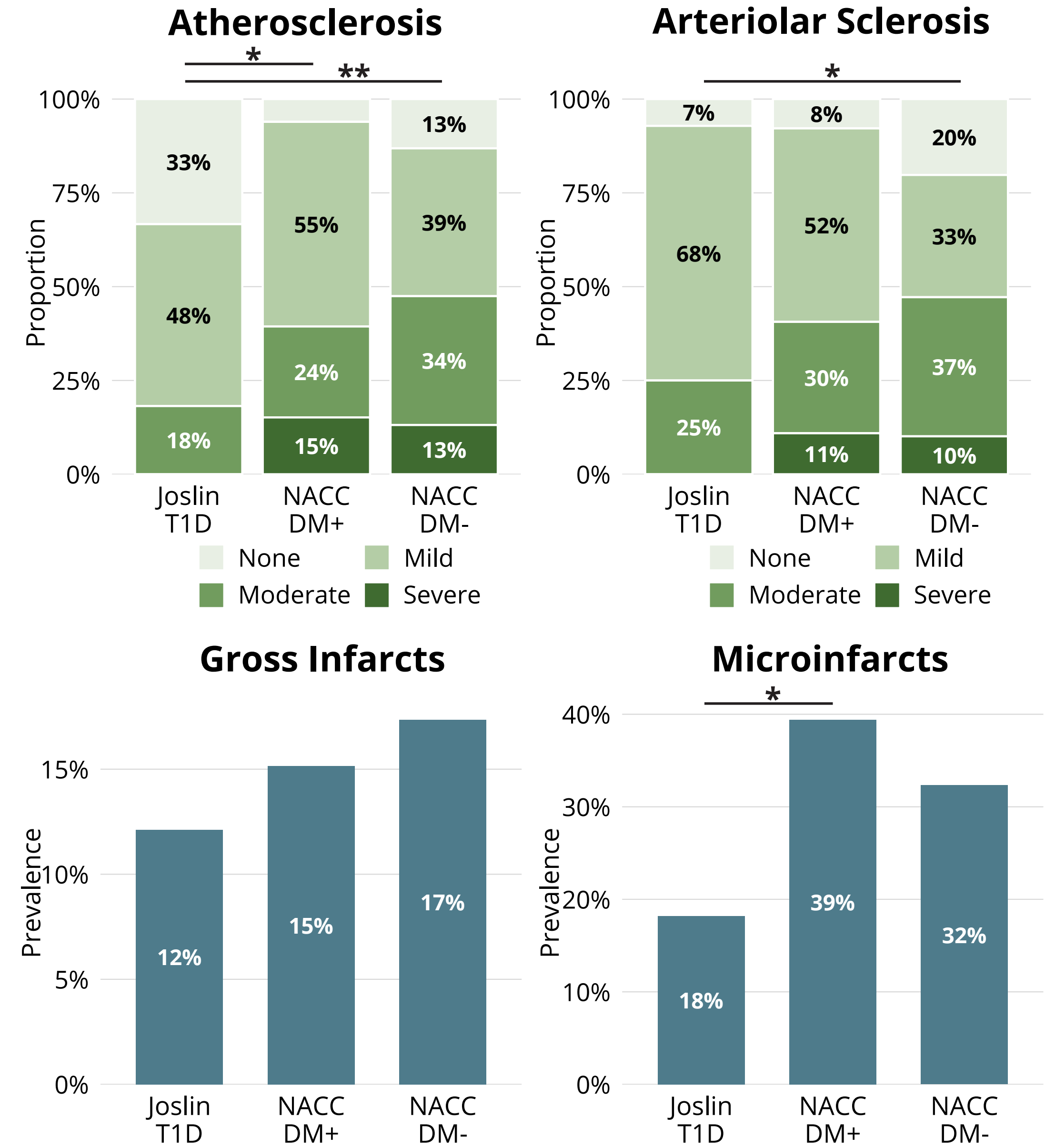
ALZHEIMER'S DISEASE NEUROPATHOLOGIC CHANGE (ADNC)



LEWY BODY DISEASE AND LATE-NC/TDP-43 PROTEINOPATHY



CEREBROVASCULAR DISEASE



CONCLUSIONS

- Long-duration T1D Medalists carry **less ADNC** than age- and sex-matched decedents with and without diabetes.
- Medalists also show **less Lewy body disease** and **less LATE-NC/TDP-43** than either comparator
- The reduced ADNC and TDP-43 pathology in T1D **mirrors findings in T2D** (Beeri 2005, Oveisgharan 2021) and extends them to insulin-deficient, non-obese siabetics.
- T1D Medalists have **less vessel wall pathology**, with less hypertensive arteriolar sclerosis than DM- comparators, and less atherosclerosis of the circle of Willis than both groups.
- There is **no cerebrovascular infarct excess** in T1D. If anything, microinfarcts are less frequent than in NACC DM+.
- The Medalists are **not a complication-free group**, which argues against a simple survivor-bias explanation.
- This suggests that **T1D differs mechanistically from T2D**. Absent hyperinsulinemia, lower BMI, and different vascular biology could shift the neurodegenerative landscape.

REFERENCES

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