

Caregiving burden, nutritional vulnerability, and plasma neurofilament light chain: a serial mediation model in older spousal caregivers

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- A higher caregiving burden led to poorer eating, lower protein in the blood, and in turn higher markers of nerve injury.
- This full chain was confirmed statistically within a single cohort, linking steps that had only been seen separately before.
- This points to a hopeful message for the clinic: supporting caregivers' nutrition may help protect their brain health.

INTRODUCTION

Why study neurodegeneration in caregivers?

Older spousal caregivers of persons with cognitive impairment are themselves at elevated risk of dementia and accelerated neurodegeneration.

Plasma **neurofilament light chain (NfL)** is a sensitive blood biomarker of neurodegeneration — the “N” of the AT(N) framework.

Yet studies linking psychological burden directly to NfL have been null or inconsistent: **burden alone may not explain NfL variation.**

A complementary hypothesis

Caregiving burden may reach neuroaxonal injury through behavioral & metabolic intermediaries.

Each link is documented, but only separately, in different populations (see Figure 1).

These links have **never been measured together in one cohort** or tested as an integrated serial mediation model.

Aim: test whether caregiving burden is associated with plasma NfL through a serial pathway **ZBI → MNA → protein → NfL**.

ZBI

MNA

Protein

NfL

Serial mediation pathway (this study)

Individual pair-link established in prior research

Serial mediation pathway tested in this study: ZBI → MNA → Protein → NfL

Figure 1. Hypothesized serial chain, with links established individually and now tested together in a serial mediation analysis.

METHODS

Design & participants

Cross-sectional analysis of an ongoing dyadic cohort (Chungnam National University).

134 older spousal caregivers; care-recipient spouses span the cognitive spectrum (CN / MCI / dementia).

Measures & analysis

Exposure: Zarit Burden Interview (ZBI)

Mediator 1: nutrition (MNA)

Mediator 2: serum total protein / albumin

Outcome: log₁₀ (plasma NfL)

Serial mediation (3 OLS equations; 5,000 bootstraps).

Table 1. Population characteristics (N = 134)

Variable	Mean ± SD or n (%)
Demographics	
Age, years	72.77 ± 6.82
Female	80 (59.7)
BMI, kg/m²	24.65 ± 3.38
Caregiver burden & nutrition	
ZBI score (0–88)	35.70 ± 20.28
MNA score (0–30)	13.85 ± 5.57
Malnourished / risk / well, %	70.1 / 25.4 / 4.5
Spouse cognitive diagnosis	
CN / MCI / Dementia, n	18 / 41 / 75
Biomarkers	
Serum total protein, g/dL	7.19 ± 0.42
Serum albumin, g/dL	4.46 ± 0.25
Plasma NfL, pg/mL	21.54 ± 16.96
Vascular risk & activity	
VRS (0–1 scale)	0.218 ± 0.164
IPAQ, MET-min/week	2,232 ± 2,267

RESULTS

Figure 2. Serial mediation path diagram (M₂ = serum total protein)

ZBI

MNA

Protein

NfL

$\beta_{01} = -0.261$
(p = 0.003)

$\beta_{02} = 0.385$
(p < 0.001)

$\beta_{03} = -0.044$
(p = 0.012)

$\beta_{04} = -0.052$ (p = 0.535)

$\beta_{05} = -0.001$ (p = 0.937)

$\beta_{06} = -0.010$ (p = 0.555)

Figure 3. Decomposition of indirect effects.

MNA

Protein

Serial indirect effect = 0.0044
95% CI [0.0007, 0.0102] (p = 0.010)

MNA-specific indirect effect = -0.0004 (p = 0.917)

Protein-specific indirect effect = 0.0023 (p = 0.517)

Total indirect = 0.0063 (p = 0.285)

ZBI

NfL

Burden reaches NfL only through the full chain

A complete, directional chain: every link was significant and in the expected direction. Higher burden predicted poorer nutrition ($\beta = -0.26$, $p = .003$), poorer nutrition predicted lower serum protein ($\beta = 0.39$, $p < .001$), and lower protein predicted higher NfL ($\beta = -0.04$, $p = .012$).

Each step is biologically grounded: these caregivers were markedly malnourished (mean MNA 13.85, within the malnourished range), and low circulating protein and albumin are established correlates of cerebral amyloid and elevated NfL.

The sequence is essential: no direct effect and no single-mediator path; the association emerged only with both mediators acting in order (0.0044 [0.0007, 0.0102], $p = .010$), which helps explain earlier null findings.

Reliable and specific: replicated with serum albumin (0.0048 [0.0012, 0.0096], $p = .006$) and robust to BMI, vascular risk, activity, and spouse cognitive diagnosis ($VIF < 1.32$).

Modest yet modifiable: the effect is small, as expected when an association passes through three sequential steps, but its value lies in actionability rather than size. It flags nutrition and circulating protein as low-cost targets that current burden-focused care overlooks, and because plasma NfL is known to improve with nutritional rehabilitation, **supporting caregivers' nutrition may help protect their brain health.**

CONCLUSIONS

Caregiving burden is linked to a neurodegeneration biomarker **indirectly**, via poorer nutrition then lower circulating protein.

A previously fragmented chain was demonstrated within a **single cohort**.

Reframes burden as a **potentially modifiable** correlate of neurodegenerative risk.

Identifies **nutrition & protein homeostasis** as low-cost, actionable targets (MNA screening)

Being cross-sectional, these are associations; longitudinal & interventional studies are now needed.

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