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Discrepancies in loneliness and social isolation predict cognitive impairment through chronic disease burden

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ABSTRACT

Background: The discrepancy between loneliness and objective social isolation (social asymmetry) has been linked to poorer cognitive aging, yet the biobehavioral pathways underlying this association remain unclear. This study tested whether chronic disease burden or allostatic load mediated associations between social asymmetry and subsequent cognitive performance.

Methods: We analyzed data from 840 adults (mean age = 54 years, range = 34–81 years) from the Midlife in the United States (MIDUS) Biomarker Project using structural equation modeling to test parallel mediation through allostatic load and chronic disease burden.

Results: Social asymmetry was associated with greater chronic disease burden but showed minimal association with allostatic load. Chronic disease burden significantly mediated relationships between social asymmetry and episodic memory and executive function, whereas allostatic load did not. ***Conclusions***: These results point to chronic disease burden, rather than allostatic load, as the primary pathway connecting social asymmetry to cognitive decline. For older adults, reducing chronic disease burden may therefore be one route to preserving cognitive function.

1. Introduction

The paradox that objective isolation and subjective loneliness can diverge has emerged as a critical factor in aging and health. Some individuals maintain emotional well-being despite limited social contact, while others experience loneliness within rich social networks (Holt-Lunstad and Steptoe, 2022; Sandy et al., 2025). This phenomenon, termed *social asymmetry* and operationalized here as residual loneliness after accounting for objective isolation, captures unique psychosocial risk (cf. McHugh et al., 2017; Ong et al., 2025). Unlike approaches that model loneliness and isolation as independent predictors, a discrepancy-based approach identifies individuals whose felt disconnection exceeds what their social contact would predict. This mismatch has been theorized to reflect persistent social threat appraisal and reduced perceived belonging, processes that may confer vulnerability to cognitive decline. Meta-analyses show both loneliness and isolation independently predict cognitive impairment with comparable effect sizes (Kuiper et al., 2015), yet the discordance between them may carry distinct risks. McHugh et al. (2017) found that older adults whose loneliness exceeded their level of isolation showed significantly poorer cognitive performance than those whose loneliness matched their isolation, suggesting the mismatch itself affects cognitive function.

Despite evidence linking social asymmetry to cognitive impairment, the mediating pathways remain unclear. Two candidate mechanisms are plausibly implicated. First, this mismatch may operate as a chronic psychosocial stressor that triggers multisystem physiological dysregulation, operationalized as allostatic load (AL), reflecting cumulative wear and tear across neuroendocrine, autonomic, metabolic, cardiovascular, and inflammatory systems (McEwen, 1998). Second, social asymmetry may promote accumulated chronic disease burden through behavioral pathways including poor self-care, delayed healthcare seeking, and maladaptive coping (Cacioppo and Hawkley, 2009;

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Holt-Lunstad et al., 2010; Valtorta et al., 2016), which in turn comprises cognitive function through established vascular and metabolic mechanisms (Barnes et al., 2012; Vassilaki et al., 2015). These pathways carry different translational implications: AL mediation would justify stress-reduction interventions, while chronic disease burden would prioritize chronic disease prevention.

The present analyses compare these pathways within a parallel framework to quantify their relative explanatory contribution.[1] Using data from 840 adults in the Midlife in the United States (MIDUS) Biomarker Project, we test whether social asymmetry at Wave 2 predicts Wave 3 episodic memory and executive function through these competing mechanisms. Sensitivity analyses in the broader MIDUS II sample (N = 4515) assess robustness under different missing-data assumptions.

2. Methods

2.1. Sample and procedures

Participants were drawn from the MIDUS study, a national longitudinal investigation of health and aging. Fig. S1 (Supplemental Materials) illustrates participant flow from the original MIDUS 1 cohort (N = 7108) through MIDUS 2 (N = 5555) and MIDUS 3 (N = 3686). The MIDUS 2 Biomarker Project invited a subset of MIDUS 2 participants to complete intensive physiological assessments; 1255 completed the biomarker protocol. The biomarker analytic sample (N = 840) included MIDUS 2 participants who completed the Biomarker Project clinic visit, provided non-missing Wave 2 loneliness and isolation measures, had Wave 3 cognitive outcomes, and had complete covariate information (missing biomarker indicators were handled per scoring protocol). All procedures were approved by the University of Wisconsin–Madison IRBs, and data are publicly available via the Inter-university Consortium for Political and Social Research (https://www.icpsr.umich.edu/icpsrweb).

2.2. Measures

Loneliness was assessed using three items adapted from the UCLA Loneliness Scale (Russell, 1996), asking how often in the past 30 days participants felt: (1) lonely, (2) close to others, and (3) a sense of belonging. Each item used a 5-point response scale ranging from 1 = all of the time to 5 = none of the time. The "close to others" and "belonging" items were reverse-coded, and the three items were averaged to form a composite score (α = .78), with higher values indicating greater loneliness. Social isolation was measured via contact frequency with neighbors, friends, and family. Neighbor contact was rated on a 6-point scale (1 = almost every day, 2 = several times a week, 3 = about once a week, 4 = two to three times a month, 5 = about once a month, 6 = never). Friend and family contact were rated on 8-point scales (1 = several times daily, 2 = about once a day, 3 = several times a week, 4 = about once a week, 5 = two to three times a month, 6 = about once a month, 7 = less than once a month, 8 = never/hardly ever). Higher scores indicated greater isolation. Both constructs have demonstrated predictive validity for health outcomes in prior MIDUS research (Ong et al., 2024, 2025) and were transformed to percent of maximum possible (POMP) scores (0–100 scale) to enable direct comparison (Cohen et al., 1999).

Social Asymmetry. Following previous research (Ong et al., 2024, 2025), social asymmetry was operationalized as the residual from regressing loneliness on isolation scores. Positive residuals indicate higher-than-expected loneliness (social vulnerability), while negative residuals represent lower-than-expected loneliness (social resilience).

Cognitive Functioning. The Brief Test of Adult Cognition by Telephone (BTACT) assessed episodic memory and executive function at Waves 2 and 3. Episodic memory was measured using immediate and delayed recall of 15 words. Executive function was assessed via inductive reasoning (number series), verbal fluency (animal naming/minute), processing speed (backward counting from 100/30 s), working memory (backward digit span), and attention switching/inhibitory control (Stop and Go Switch Task). The BTACT has shown adequate reliability, validity, and sensitivity to cognitive changes across midlife and older adulthood (Lachman and Tun, 2008; Tun and Lachman, 2006).

Mediators. Wave 2 mediators examined health pathways linking social asymmetry to cognition. Chronic disease burden was defined as the number of self-reported chronic conditions at Wave 2 (e.g., hypertension, diabetes, cancer, heart disease, respiratory illness). AL was derived from 24 biomarkers spanning seven systems: cardiovascular (blood pressure, heart rate), lipid (waist–hip ratio, triglycerides, high-density lipoprotein [HDL], low-density lipoprotein [LDL]), glucose (hemoglobin A1c [HbA1c], glucose, homeostatic model assessment for insulin resistance [HOMA-IR]), inflammation (C-reactive protein [CRP], fibrinogen, interleukin-6 [IL-6], soluble E-selectin [sE-selectin], soluble intercellular adhesion molecule-1 [sICAM-1]), sympathetic (urine epinephrine/norepinephrine), hypothalamic-pituitary-adrenal (HPA; urine cortisol, dehydroepiandrosterone sulfate [DHEA-S]), and parasympathetic (heart rate variability [HRV] indices). Biomarkers with marked positive skew ($>|1.5|$) (e.g., CRP, IL-6, triglycerides, HbA1c, glucose, HOMA-IR, sE-selectin, sICAM-1, and urinary cortisol/catecholamines) underwent Box–Cox transformation to approximate normality; biomarkers without substantial skew (blood pressure, heart rate, waist-hip ratio, HDL, LDL, glucose, fibrinogen, DHEA-S, and HRV indices) were retained on their original scale. Participants using medications for hypertension, hyperlipidemia, or diabetes were assigned a score of 1 for the respective system (Woo et al., 2020). High-risk quartiles (lowest for HDL) were coded as 1, otherwise 0, and system risk indices reflected the proportion of biomarkers per system in high-risk quartiles (Gruenewald et al., 2009).

Covariates. Models adjusted for age (years), gender (0 = male, 1 = female), education (years), and race/ethnicity. Race was categorized as White (reference), Black, or Additional Race, with the latter combining Native American/Alaska Native, Asian, Pacific Islander, and other groups due to small cell sizes.

2.3. Statistical analysis

Analyses used structural equation modeling (SEM) in the *lavaan* package in R (Rosseel, 2012). Model 1 estimated total effects of Wave 2 social asymmetry on Wave 3 cognition, adjusting for baseline cognition and covariates. Model 2 added chronic disease burden and AL as parallel mediators. Episodic memory and executive function were modeled jointly with correlated residuals. All models adjusted for baseline cognition, age, gender, education, and race. Model fit was evaluated with χ^2, comparative fit index (CFI; $\geq$0.95), root mean square error of approximation (RMSEA; $\leq$0.08), and standardized root mean square residual (SRMR; <0.08) (Hu and Bentler, 1999). Indirect effects were estimated using 5000 bootstrap samples (Cheung, 2007; Hayes, 2018).

Chronic disease burden and AL were modeled in parallel to compare the relative explanatory contribution of two candidate pathways measured at the same wave. The model does not assume that these mediators are causally independent; their residuals were allowed to correlate to account for shared variance.

2.4. Sensitivity analysis

Primary analyses were conducted in the Wave 2 biomarker subsample (N = 840) including participants with complete data on both mediators and Wave 3 outcomes. Full information maximum likelihood

[1] Because allostatic load and chronic disease burden were assessed contemporaneously at Wave 2, the analyses do not impose a serial ordering (e.g., allostatic load → chronic disease burden or the reverse), which would require stronger temporal assumptions than the design can support.

(FIML) was applied only to missing covariates (Enders and Bandalos, 2001). This complete-case approach ensures that AL mediation estimates reflect observed biomarker data. Given selective participation in the biomarker module, these models are treated as primary.

Sensitivity analyses used a larger sample of eligible MIDUS II participants ($N = 4515$) and incorporated FIML for missing mediators/outcomes under a missing-at-random (MAR) assumption. Balance between the analytic and sensitivity samples was evaluated using standardized mean differences (SMDs); all baseline characteristics showed negligible differences ($|d| < 0.30$; see Table S2), suggesting minimal selection bias (Austin, 2009; Stuart et al., 2013). Because the MAR assumption is untestable and potentially violated given selective biomarker participation and mortality-related attrition, sensitivity estimates are treated as supplementary to the complete-case results.

3. Results

3.1. Descriptive statistics

The analytic sample ($N = 840$) had a mean age of 53.86 years ($SD = 10.88$) and was 57% female. Most participants (92%) identified as White, with 3% Black and 5% other racial/ethnic groups. Participants averaged 2.18 chronic conditions ($SD = 2.14$, range = 0–16). Mean AL was 2.30 ($SD = 1.15$). Social asymmetry scores were normally distributed ($M = -0.05$, $SD = 1.00$). At Wave 3, episodic memory averaged 0.06 ($SD = 0.98$) and executive function −0.03 ($SD = 0.68$); baseline Wave 2 scores were similar (episodic: $M = 0.16$, $SD = 0.88$; executive: $M = 0.27$, $SD = 0.85$). Full descriptive statistics are provided in Table S1 (see Table 1).

3.2. Social asymmetry, chronic disease burden, and cognition

Structural equation models demonstrated adequate fit (CFI = 0.98, SRMR = 0.02, RMSEA = 0.069 [90% CI: 0.045, 0.096]). Higher social asymmetry at Wave 2 was associated with higher chronic disease burden ($\beta_{std} = 0.59$, $p < .001$) but was not significantly associated with AL ($\beta_{std} = 0.08$, $p = .062$). Higher chronic disease burden was associated with poorer Wave 3 episodic memory ($\beta_{std} = -0.04$, $p = .016$), and AL showed a significant direct association with executive function ($\beta_{std} = -0.03$, $p = <.05$). Indirect effects through chronic disease burden were significant for episodic memory ($\beta_{std} = -0.02$, $p = .024$), whereas indirect effects through AL were nonsignificant (episodic memory: $\beta_{std} = -0.003$, $p = .31$; executive function: $\beta_{std} = -0.002$, $p = .35$). Total effects confirmed that higher social asymmetry was associated with poorer cognitive performance (see Table 2). Fig. 1 illustrates the decomposition of total, direct, and indirect effects.

3.3. Sensitivity analyses

In the larger MIDUS sample ($N = 4515$), FIML models replicated the chronic disease burden mediation pattern and again showed no significant AL mediation. Model fit was good (CFI = 0.98, SRMR = 0.02, RMSEA = 0.056 [90% CI: 0.046–0.066]). Social asymmetry was associated with higher chronic disease burden ($\beta_{std} = 0.58$, p < .001) and higher AL ($\beta_{std} = 0.09$, $p = .019$). Higher chronic disease burden predicted poorer Wave 3 episodic memory ($\beta_{std} = -0.02$, $p = .011$) and executive function ($\beta_{std} = -0.01$, $p = .029$). Indirect effects through chronic disease burden were significant for both outcomes (episodic: $\beta_{std} = -0.01$, $p = .012$; executive: $\beta_{std} = -0.01$, $p = .030$), while AL pathways remained nonsignificant, replicating the main results (see Table S3).

Table 1
Descriptive statistics (N = 840).

Variable	Mean	SD	Min	Max	%Missing
Social Asymmetry	−0.05	1.00	−1.97	3.84	0.00
Chronic Disease Burden	2.18	2.14	0.00	16.00	0.00
Allostatic Load	2.30	1.15	0.00	6.17	0.00
Episodic Memory (Wave 3)	0.06	0.98	−2.50	3.64	0.00
Executive Function (Wave 3)	−0.03	0.68	−2.94	1.97	0.00
Age	53.86	10.88	34.00	81.00	0.00
Female	0.57	0.50	0.00	1.00	0.00
Education	7.85	2.42	1.00	12.00	0.12
Black	0.03	0.16	0.00	1.00	0.12
Other	0.05	0.21	0.00	1.00	0.00
Episodic Memory (Wave 2)	0.16	0.88	−2.19	3.37	3.81
Executive Function (Wave 2)	0.27	0.85	−2.12	2.92	3.57

Table 2
Model Fit and Standardized Effects for Total and Mediation Models Predicting Wave 3 Cognitive Outcomes for Outcome and Mediator Complete-Case analysis.

Outcome/Predictor	Model 1: Total Effects	Model 2: Parallel Mediation
	B_{std} (SE)	B_{std} (SE)
Episodic Memory (Wave 3)		
Social Asymmetry	−.02(.03)	−.00(.02)
Episodic Memory (Wave 2)	.43(.04)***	.43(.04)***
Age	−.23(.03)***	−.23(.04)***
Female	.38(.06)***	.41(.05)***
Education	.09(.03)***	.09(.03)***
Black (ref. = White)	−.19(.18)	−.19(.13)
Other Race (ref. = White)	.17(.13)	.17(.16)
Chronic Disease Burden		−.04(.02)*
Allostatic Load		.03(0.03)
Indirect Chronic Disease Burden		−.02(.01)*
Indirect Allostatic Load		−.003(.003)
Total Indirect		−.02(.01)*
Total		−0.02(.03)
Executive Function (Wave 3)		
Social Asymmetry	−.02(.02)	−.01(.02)
Executive Function (Wave 2)	.50(.02)***	.50(.02)***
Age	−.17(.02)***	−.17(.02)***
Female	−.09(.03)***	−.09(.03)***
Education	.05(.02)***	.05(.02)***
Black (ref. = White)	−.10(.09)	−.10(.10)
Other Race (ref. = White)	−.05(.07)	−.05(.06)
Chronic Disease Burden		−0.01(.01)
Allostatic Load		−.03(.01)*
Indirect Chronic Disease Burden		−.003(.01)
Indirect Allostatic Load		−.002(.002)
Total Indirect		−.01(.01)
Total		−.02(.02)
Model Fit		
χ^2 (df), p	16.55 (2), $p < .01$	29.69 (6), $p < .01$
CFI	.99	.98
TLI	.89	.89
RMSEA [90% CI]	.093 [0.055, 0.137]	.069 [0.045, 0.096]
SRMR	.015	.019
N	840	840

Note. B_{std} = Standardized coefficient; SE = Standard Error; CFI = Comparative Fit Index; TLI = Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual; N = Sample Size; df = Degrees of Freedom; ref. = Reference; *$p < .05$, **$p < .01$, ***$p < .001$; Direct effects represent the association between each predictor and cognitive outcomes controlling for other variables. Indirect effects represent the mediation pathway (social asymmetry → mediator → cognition).

4. Discussion

The present findings indicate that chronic disease burden, rather than AL, mediated the association between social asymmetry and cognitive performance. Previous research has established that accumulated chronic conditions compromise cognitive function through vascular and metabolic mechanisms (Barnes et al., 2012; Vassilaki et al., 2015); our results identify chronic disease burden as a specific pathway linking social asymmetry to later cognitive outcomes.

The absence of a statistically detectable indirect effect through the

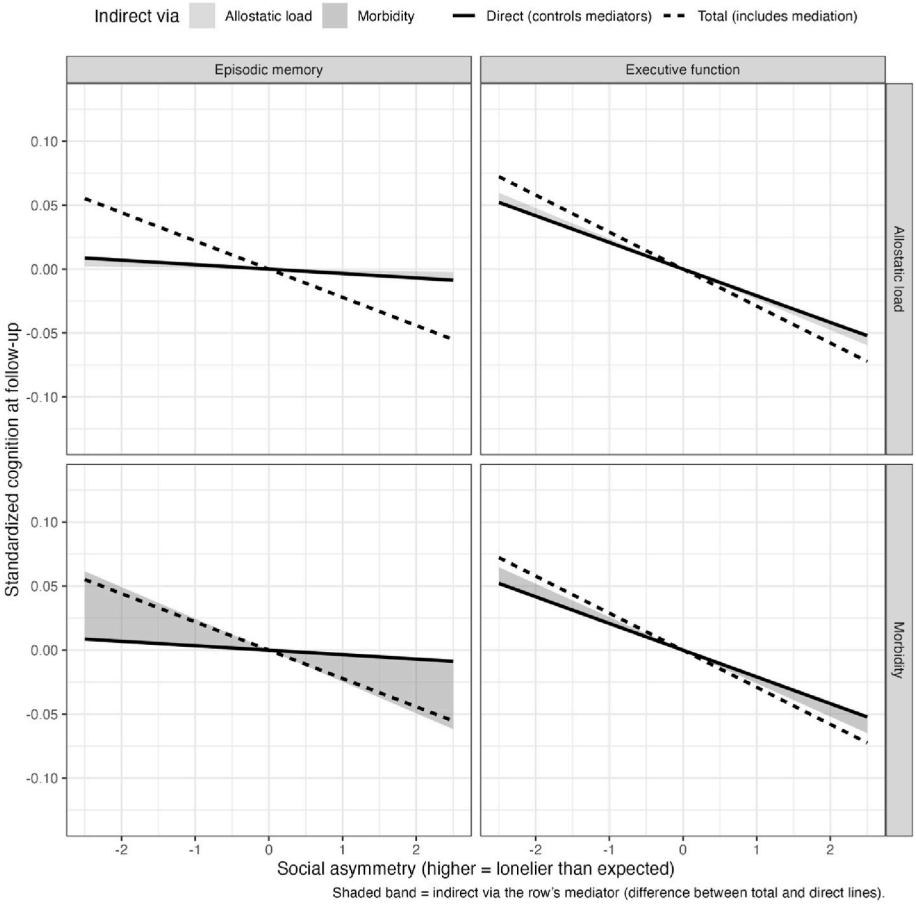

Fig. 1. Decomposition of Total, Direct, and Indirect Effects of Social Asymmetry on Cognitive Outcomes

Note. Panels show predicted follow-up cognition (standardized) as a function of social asymmetry (x-axis; units = SDs, negative = less lonely than expected, positive = more lonely). Solid lines depict the direct association of social asymmetry with cognition controlling for both mediators; dashed lines show the total association (direct + indirect). The shaded area represents the indirect effect through the row's mediator—the vertical gap between total and direct lines—so greater shading indicates stronger mediation. The direction of the effect shows whether mediation amplifies or reduces the overall association.

AL composite should not be interpreted as evidence that stress-related physiology is irrelevant. The null finding may reflect several design- and measurement-consistent possibilities. Associations between psychosocial exposures and multisystem AL composites may be modest in magnitude, particularly when measured with brief social indicators and aggregated across heterogeneous physiological subsystems (Yoneda et al., 2023). AL was assessed at a single time point, and effects of social asymmetry may require sustained or repeated exposure before manifesting as detectable dysregulation (Booth et al., 2015). Composite indices can reduce pathway specificity by pooling across systems; cognition-relevant neuroimmune activity (e.g., IL-6, CRP) may be partially obscured when subsumed within a broad index rather than examined as inflammation-focused specifications. Finally, participation in the biomarker clinic may introduce positive health selection, restricting variance in AL and reducing power to detect indirect effects. The null indirect effect is therefore indeterminate with respect to mechanism.

The mediation through chronic disease burden is consistent with multiple pathways to cognitive impairment. Vascular disease contributes to small vessel damage that disrupts neural networks supporting memory and executive function (Wardlaw et al., 2019). Chronic inflammation elevates cytokines that promote neuroinflammation (Heneka et al., 2015), while metabolic dysfunction impairs neuronal energy metabolism, synaptic plasticity, and increases amyloid buildup (Arnold et al., 2018). Managing multiple conditions may also limit cognitive and social engagement (Marengoni et al., 2011). Each additional condition compounds risk through overlapping biological and behavioral mechanisms (Vassilaki et al., 2015). Behavioral pathways, including physical activity, sleep, medication adherence, healthcare engagement, and cardiometabolic risk management, are also plausible contributors to the social asymmetry–disease burden association and warrant direct measurement in future studies.

5. Strengths and limitations

This study draws on a nationally representative cohort with objective biomarkers and validated cognitive measures, but several limitations warrant consideration. Because MIDUS is a secondary dataset, some theoretically relevant covariates and time-varying processes were not measured. Chronic disease burden and AL were assessed at Wave 2, but cognitive outcomes were assessed at Wave 3. Changes in disease status or physiology occurring between waves are therefore unobserved and may bias pathway estimates. These findings should be interpreted as longitudinal associations conditioned on baseline cognition and demographic covariates, not as evidence of causal timing.

The residual-based operationalization of social asymmetry assumes that loneliness variance unexplained by isolation reflects a meaningful discrepancy rather than measurement error or third-variable confounding. However, these residuals may partly reflect stable psychological traits (e.g., neuroticism, depressive tendencies, or negative perceptions of relationship quality) that independently predict both elevated loneliness and poorer cognitive outcomes. Future research should include personality and mental health indicators to parse these overlapping constructs.

Marital status was not included as a covariate because it may lie on the causal pathway between social asymmetry and health outcomes; marriage affects both objective social contact and subjective loneliness. Our social isolation measure already captures family contact frequency, partially indexing partnership effects, but unmeasured aspects of relationship quality or partnership status could contribute to residual confounding.

As discussed above, the composite AL index trades pathway specificity by pooling across systems. Inflammation-specific markers (e.g., IL-6, TNF-α, CRP) examined independently may be more sensitive to the neuroimmune mechanisms most relevant to cognition. Future work should test inflammation-focused and disease-specific specifications (e.g., comparing cardiovascular, metabolic, and inflammatory conditions separately) to clarify which pathways most strongly link social asymmetry to cognitive decline. Direct measurement of behavioral mechanisms, including healthcare use, medication adherence, and lifestyle factors, would also help account for the social asymmetry–disease burden association. Intervention studies are needed to determine whether managing chronic conditions more effectively preserves cognitive function compared to psychosocial interventions alone.

6. Conclusion

Social asymmetry was associated with poorer cognitive performance primarily through chronic disease burden, suggesting that individuals who report loneliness despite adequate social contact may benefit from closer chronic disease monitoring. Screening for loneliness assessment with chronic disease management could help identify individuals whose cognitive health is at greatest risk. Wheather disease prevention is more effective than stress-focused intervention for preserving cognition remains an open question requiring direct expertimental comparison.

CRediT authorship contribution statement

Dakota W. Cintron: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Tomiko Yoneda:** Writing – review & editing, Writing – original draft, Methodology. **Hebi Wang:** Writing – review & editing, Methodology. **Eileen K. Graham:** Writing – review & editing. **Anthony D. Ong:** Writing – review & editing, Writing – original draft, Conceptualization.

Author note

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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This work was completed while A. D. Ong was on sabbatical leave at Harvard University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2026.101232.

Data availability

Data will be made available on request.

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