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**RESEARCH LETTER****Multi-level social determinants of health, inflammation, and postoperative delirium in older adults**

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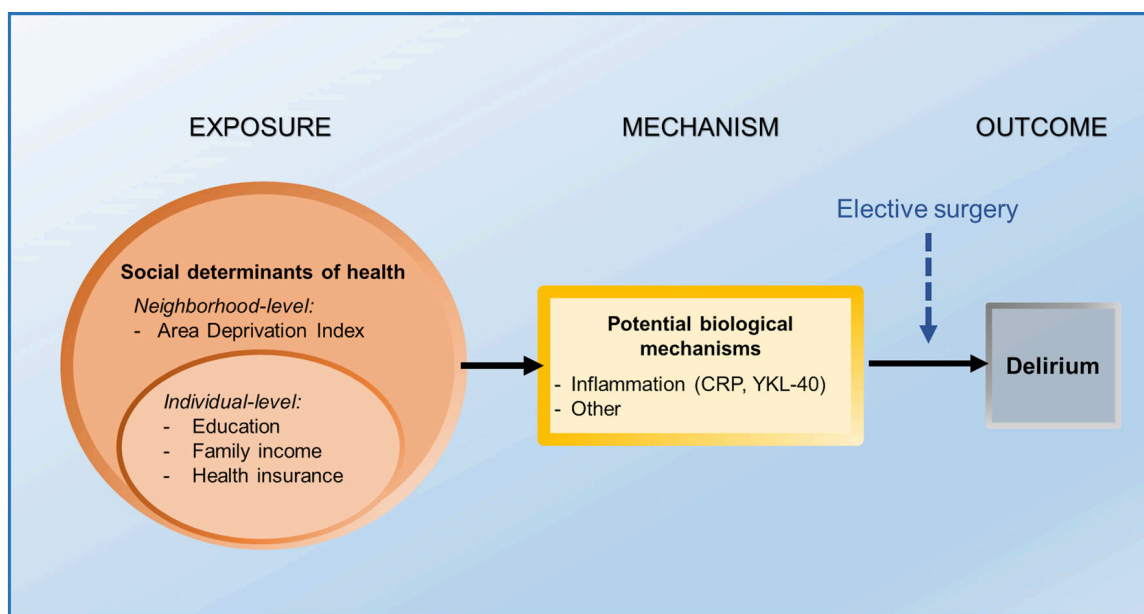
**INTRODUCTION**

Social determinants of health (SDOH) have been associated with numerous medical conditions, including postoperative delirium—a common, morbid, and costly geriatric syndrome characterized by an acute confusional state.<sup>1</sup> Individual-level SDOH (e.g., lower income) and neighborhood-level SDOH (e.g., greater area deprivation index [ADI]) have been associated with greater delirium incidence and severity<sup>2,3</sup>; however, the underlying biological mechanisms linking these factors remain unclear.

Based on our conceptual model (see Figure 1), we hypothesize that multilevel SDOH (i.e., neighborhood-level SDOH [ADI] vs individual-level SDOH [education, family income, and health insurance]) elicit biological changes (e.g., higher systemic inflammation) that may increase risk of delirium in older adults after major surgery. Specifically, we test the hypothesis that preoperative systemic inflammation will explain at least some of the association between multiple measures of SDOH and delirium.

Sharon K. Inouye and Amy J. H. Kind are co-senior authors.





**FIGURE 1** Conceptual model. Area deprivation index calculated based on the 2009–2013 American Community Survey 5-year averages. Source: Neighborhood Atlas.<sup>10</sup> CRP, C-reactive protein; YKL-40, chitinase 3-like protein (CHI3L1/YKL-40).

## METHODS

We examine participants age  $\geq 70$  undergoing major, noncardiac surgery enrolled in the Successful Aging after Elective Surgery (SAGES) study ( $N = 553$  with data for SDOH, inflammation, and delirium measures).<sup>4</sup> We consider two groups of SDOH (see Figure 1): neighborhood-level and individual-level factors (as dichotomous variables, based on prior literature)—(1) neighborhood/social exposome level: ADI  $> 44$  versus  $< 44$ <sup>2</sup>; and (2) individual level: education  $\leq 12$  versus  $> 12$  years (aligns with high school completion), household income  $< \$20,000$  versus  $\geq \$20,000$  (aligns with the federal poverty level; see Table 1 footnote for additional details), and private health insurance (present/absent). We additionally consider a composite measure indicating the presence of any individual-level disadvantage factor (education  $\leq 12$ , income  $< \$20,000$ , or no private health insurance). Based on prior work identifying key preoperative plasma-based predictors of postoperative delirium,<sup>5,6</sup> we used a log-transformed, weighted combination of C-reactive protein (CRP) and chitinase 3-like protein (CHI3L1/YKL-40) to summarize inflammation<sup>7</sup> for the present analysis.

Applying logistic regression models within the R ExactMed package,<sup>8</sup> we assess the association between these exposure variables and delirium (incidence) in two sets of models: (1) “base model” (total effect) which includes each SDOH measure in separate models; and (2) a “base model + inflammation” that reports a direct effect (effect of SDOH on delirium absent inflammation) and an indirect effect (effect of SDOH on delirium that

works through inflammation). We report odds ratios (OR), 95% confidence intervals,  $p$ -values, and the percent change in regression parameters between the direct effect and total effect OR.

## RESULTS

Adverse individual-level and neighborhood-level SDOH are associated with risk for greater postoperative delirium (see Table 1, base models). For example, the OR for the neighborhood-level measure ADI is 3.20 and the individual-level measure private health insurance is 2.38. We illustrate smaller ORs for all individual-level SDOH “base + inflammation” direct effects (e.g., OR 2.01 for private health insurance); however, this is not observed for ADI, where the OR increased to 3.35. The change in the OR, which approximates the mediation effects of inflammation, is most pronounced for the individual-level factors. The decrease in the OR between the direct and total effect for the individual-level SDOH are  $-15.5\%$  for private health insurance,  $-9.1\%$  for presence of any individual-level disadvantage factor,  $-6.9\%$  for education, and  $-4.3\%$  for household income. In contrast, a positive change in the OR is observed for the neighborhood-level measure ADI (4.7%).

## DISCUSSION

These preliminary findings suggest that preoperative inflammation may explain, in part, the association

TABLE 1 Association of multi-level social determinants of health and delirium incidence.

Multi-level social determinants of health risk factors	Delirium (yes/no)	Base model (total effect)						Base model + inflammation <sup>b</sup> (direct effect)						Base model + inflammation <sup>b</sup> (indirect effect)					
		Odds ratio		95% CI		p-Value		Odds ratio		95% CI		p-Value		Odds ratio		95% CI		p-Value	
		n (%) <sup>a</sup>																	
<b>Neighborhood level</b>																			
ADI <sup>c</sup> >44 versus ≤44	25 (5)	3.20	(1.43–7.18)	>0.01	3.35	(1.44–7.75)	<0.01	1.04	(0.83–1.30)	0.72	4.7								
<b>Individual level</b>																			
Education ≤12 versus 12 years	158 (29)	1.30	(0.85–1.99)	0.22	1.21	(0.78–1.87)	0.40	1.09	(0.98–1.21)	0.10	–6.9								
Household income <\$20k versus ≥\$20k	59 (12)	1.84	(1.03–3.29)	0.04	1.76	(0.96–3.20)	0.07	1.08	(0.93–1.25)	0.29	–4.3								
Private health insurance (no vs yes)	36 (7)	2.38	(1.20–4.73)	0.01	2.01	(0.99–4.10)	0.05	1.24	(1.02–1.50)	0.03	–15.5								
Presence of any individual-level risk factor <sup>d</sup>	202 (37)	1.54	(1.03–2.30)	0.03	1.40	(0.93–2.12)	0.11	1.12	(1.01–1.24)	0.03	–9.1								

Note: N = 553. "Base model" uses logistic regression to assess the association between each social determinant of health and delirium. Abbreviations: ADI, area deprivation index; CI, confidence interval.

<sup>a</sup>For the first listed group (i.e., ADI > 44,<sup>2</sup> education ≤12 years, income <\$20k, no private health insurance).

<sup>b</sup>Lasso-derived inflammation index for delirium at PREOP.

<sup>c</sup>ADI calculated based on the 2009–2013 American Community Survey 5-year averages. ADI > 44 adopted based on previously identified cutpoint.<sup>2</sup> Source: Neighborhood Atlas.<sup>10</sup>

<sup>d</sup>≤12 years of education or <\$20,000 household income or no private insurance. Based on the 2022 federal poverty level: \$18,310 for family of 2; \$27,750 for family of 4 (<https://www.healthcare.gov/glossary/federal-poverty-level-fpl/>).

between individual-level SDOH and delirium, whereas biological factors other than inflammation may link the neighborhood-level SDOH to delirium. Potential explanations include (1) neighborhood-level factors (e.g., ADI) are likely influenced by many different external/environmental measures (e.g., environmental pollutants and chemical contaminants), whereas individual-level factors (e.g., education) may be less dependent on external/environmental measures; or (2) neighborhood-level SDOH captures different potential health vulnerabilities than individual-level SDOH.<sup>9</sup>

This study is novel in highlighting the possibility that different biological pathways may be triggered by different levels of SDOH (individual-level vs neighborhood-level). Our findings underscore the need to explore additional biologic pathways to better understand the mechanistic underpinnings of SDOH on delirium. Future studies in larger surgical cohorts could inform promising, clinically actionable interventions, such as targeting patients who may benefit most from well-established interventions to prevent delirium, which poses major threats to quality-of-life for older adults.

#### AUTHOR CONTRIBUTIONS

*Study concept and design:* Sarinnapha M. Vasunilashorn, Emily Wolfson, Miles Berger, Jacqueline Leung, Erin B. Ware, Andrea Baccarelli, Richard N. Jones, Long H. Ngo, Edward R. Marcantonio, Sharon K. Inouye, and Amy J. H. Kind. *Acquisition of subjects and data:* Richard N. Jones, Long H. Ngo, Edward R. Marcantonio, and Sharon K. Inouye. *Analysis and interpretation of data:* Sarinnapha M. Vasunilashorn, Emily Wolfson, Miles Berger, Jacqueline Leung, Erin B. Ware, Andrea Baccarelli, Richard N. Jones, Long H. Ngo, Edward R. Marcantonio, Sharon K. Inouye, and Amy J. H. Kind. *Preparation of manuscript:* Sarinnapha M. Vasunilashorn, Emily Wolfson, Miles Berger, Jacqueline Leung, Erin B. Ware, Andrea Baccarelli, Richard N. Jones, Long H. Ngo, Edward R. Marcantonio, Sharon K. Inouye, and Amy J. H. Kind.

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#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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None of the sponsors were involved in the design, methods, subject recruitment, data collection, analysis, or preparation of the article.

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