Residential proximity to major roadways and renal function

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ABSTRACT

Background Living near major roadways has been associated with increased risk of cardiovascular events, but little is known about its impact on renal function.
Methods We calculated the estimated glomerular filtration rate (eGFR) for 1103 consecutive Boston-area patients hospitalised with confirmed acute ischaemic stroke between 1999 and 2004. We used linear regression to evaluate the association between eGFR and categories of residential distance to major roadway (0 to ≤50, >50 to ≤100, >100 to ≤200, >200 to ≤400, >400 to ≤1000 and >1000 m) adjusting for age, sex, race, smoking, comorbid conditions, treatment with ACE inhibitor and neighbourhood-level socioeconomic characteristics. In a second analysis, we considered the log of distance to major roadway as a continuous variable.
Results Patients living closer to a major roadway had lower eGFR than patients living farther away (P_{trend}=0.01). Comparing patients living 50 m versus 1000 m from a major roadway was associated with a 3.9 ml/min/1.73 m^2 lower eGFR (95% CI 1.0 to 6.7; p=0.007): a difference comparable in magnitude to the reduction in eGFR observed for a 4-year increase in age in population-based studies. The magnitude of this association did not differ significantly across categories of age, sex, race, history of hypertension, diabetes or socioeconomic status.
Conclusions Living near a major roadway is associated with lower eGFR in a cohort of patients presenting with acute ischaemic stroke. If causal, these results imply that exposures associated with living near a major roadway contribute to reduced renal function, an important risk factor for cardiovascular events.

INTRODUCTION

Ambient air pollution is a recognised risk factor for cardiovascular disease.[1] There is evidence that living near a major roadway contributes to the incidence of vascular disease[1 2] including increased cardiovascular mortality,[3–5] acute myocardial infarction,[6] adverse prognosis among early survivors of acute myocardial infarction,[7] atherosclerosis as indicated by increased coronary artery calcium[8] and peripheral arterial disease[9] and deep vein thrombosis.[10]

The kidney is a highly vascularised organ susceptible to both large vessel artherosclerotic disease and small vessel dysfunction. Given the detrimental effects of residential proximity to major roadway in other vascular beds, living near a major roadway may also be associated with impaired renal function. Impaired renal function, as assessed by estimated glomerular filtration rate (eGFR), is associated with an increased risk of acute cardiovascular events and death,[11 12] and may potentially underlie, at least partly, the observed association between traffic pollution and cardiovascular risk. We hypothesised that living near a major roadway would be associated with impaired renal function as assessed by eGFR. We examined this hypothesis in a convenience sample of 1103 consecutive patients presenting with acute ischaemic stroke in the Boston metropolitan region.

METHODS

Study population

This study was approved by the Committee on Clinical Investigations (Institutional Review Board) at the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts. The study population consisted of consecutive patients ≥21 years of age, residing in the Boston metropolitan region and admitted to the BIDMC between 1 April 1999 and 31 December 2004, with a confirmed acute ischaemic stroke, as previously described.[13]

eGFR estimation

Serum creatine at the time of hospital presentation (and therefore, prior to any diagnostic imaging related to the index admission) was measured by the clinical chemistry laboratory photometrically using the Jaffe reaction, with a coefficient of variation of 6.4% at the level of 0.7 mg/dl and 2.2% at the level of 5.6 mg/dl. We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows:[14]

$$\mathrm{eGFR} = 141 \times \min(\mathrm{Scr}/\kappa, 1)^{\alpha} \times \max(\mathrm{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018\,(\text{if female}) \times 1.159\,(\text{if black})$$

where *eGFR* represents the estimated GFR in ml/min/1.73 m^2, Scr represents measured serum creatine, κ is 0.7 for women and 0.9 for men, α is −0.329 for women and −0.411 for men, min denotes the minimum of Scr/κ or 1 and max denotes the maximum of Scr/κ or 1. This equation was developed in a population consisting of patients with and without CKD, using pooled data on 8254 patients from 10 research studies, and validated on an additional 3896 patients from 16 studies.[14] The CKD-EPI equation has been found to provide more accurate cardiovascular risk prediction than the Modification of Diet in Renal Disease Study equation.[15]

Exposure assessment

We used ArcGIS (V.9.2; ESRI Inc, Redlands, California, USA) to geocode patients' addresses. We calculated the distance from the residence to the nearest major roadway with major roadways defined as those roads having US Census Feature Class Code A1 (primary highway with limited access) or A2 (primary road without limited access), as in previous studies.[7 16]

Covariate assessment

For each patient, trained abstractors recorded data on patient demographics and medical history from patient charts or electronic medical records using standardised forms, as previously described.[13] Race was categorised as white, black or other. We used area-based measures of income and educational attainment available from the 2000 US Census as measures of neighbourhood-level socioeconomic status. Both the median household income in 1999 and the percentage of people ≥25 years of age whose highest completed educational degree was below high school were determined at the census block group level, and we assigned these values to each patient according to their location of residence.

Statistical analysis

We used linear regression to evaluate the cross-sectional association between residential distance to major roadway and eGFR. As in previous studies,[8] we first considered the categories of distance to major roadway (0 to ≤50, >50 to ≤100, >100 to ≤200, >200 to ≤400, >400 to ≤1000 and >1000 m) and estimated the adjusted mean eGFR for each category. These categories, with narrower bounds for more proximal distances, were chosen to reflect the approximately exponential decay function relating traffic pollution and noise as distance from roadway increases.[17–19] Tests for the linear component of trend were performed by assigning each exposure category the natural log of the median distance within each category and including the term as a continuous variable in the regression model. The p value obtained represents the linear component of trend. To verify that our results were not sensitive to the choice of categories, we repeated this analysis considering fewer categories of distance to major roadway (≤100, 100 to ≤300, >300). Additionally, we modelled the association between eGFR and the natural logarithm of residential distance to major roadway as a continuous variable. We present the results from this model by contrasting patients living 50 m to the nearest major roadway to those living 1000 m from the nearest major roadway, calculated as $\ln(1000)\times\beta-\ln(50)\times\beta$, where β denotes the β coefficient from the linear regression model treating log of distance to roadway as a linear continuous variable. This contrast reflects the mean adjusted difference in eGFR between subjects likely to have high levels of exposure to traffic-related pollution versus those exposed to levels indistinguishable from background. Since A1 and A2 roads may represent different exposures, we also estimated the association between eGFR and the natural logarithm of residential distance to nearest A1 or A2 roadway, separately and jointly.

To further characterise the functional form of the relationship between residential distance to the nearest major roadway and eGFR, we also modelled the natural logarithm of distance to the nearest major roadway as a continuous variable using penalised splines (Greenland 1995). A priori, we selected 2 degrees of freedom based on biological plausibility; in these data, this was also consistent with the number of degrees of freedom that minimised the Akaike Information Critierion for the fitted model.

In all models, we controlled for potential confounding by age (continuous), sex, race (white, black or other), smoking status (current, former or never), history of diabetes, hypertension, heart failure or coronary artery disease, current treatment with ACE inhibitor (ACEI) and census block level estimates of median household income (continuous) and percentage of residents ≥25 years of age without a high school diploma (continuous). We chose to adjust for current treatment with ACEI since in some patient populations ACEI use is associated with lower levels of GFR. These confounders were selected a priori. As a sensitivity analysis, we repeated these analyses excluding 30 (2.7%) patients with eGFR<15 ml/min/1.73 m^2, the clinical cutoff for stage 5 CKD. Adjusted mean levels of eGFR were computed using the LSMEANS option in PROC GLM in SAS.

We examined whether the association between distance to major roadway and eGFR varied across subgroups defined by age (<70 vs ≥70 years), sex, race (white vs other), history of diabetes, history of hypertension and neighbourhood median household income (≤\$50 000 vs >\$50 000) by adding interaction terms into separate regression models. Statistical significance of interaction was assessed using the Wald test for the interaction terms.

A p value of <0.05 (two-sided) was considered statistically significant. Statistical analyses were performed using SAS (V.9.2; SAS Institute Inc, Cary, North Carolina, USA) and R 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between 1999 and 2004, 1120 patients were hospitalised at the BIDMC with a confirmed acute ischaemic stroke. Data on residential address and serum creatinine at the time of hospital presentation were available in 98.5% (n=1103) of these patients. Patients were elderly and predominantly women and white (table 1). Patients living closer to major roadways tended to be older, were more likely to be men and were less likely to be white compared with patients living further from major roadways. Consistent with the urban location of this study, just over half of the patients lived within 1 km of a major roadway with the remainder living between 1 and 10 km from a major roadway (figure 1). Mean eGFR levels were 66.4 (SD: 24.8, 25th percentile: 48.9, 75th percentile: 83.8) ml/min/1.73 m^2 with the lowest levels observed among participants living closest to major roadways (table 1).

In models adjusting for patient demographics, medical history and neighbourhood-level measures of socioeconomic status, mean eGFR was lower among patients living closer to a major roadway as compared with patients living further away (figure 2; P_{trend}=0.01). Results were similar in a sensitivity analysis where we modelled residential distance to the nearest major roadway in three categories (P_{trend}=0.03; see online supplementary figure 1) and when we modelled the natural logarithm of distance to roadway as a continuous variable (table 2). In fully adjusted models, eGFR levels among patients living 50 m from the nearest major roadway were an average of 3.9 ml/min/1.73 m^2 (95% CI 1.0 to 6.7) lower than the eGFR levels of patients living 1000 m from the nearest major roadway. The results were not materially different in sensitivity analyses excluding patients with stage 5 CKD (eGFR <15 ml/min/1.73 m^2; see online supplementary figure 2 and supplementary table 1). In additional sensitivity analyses, eGFR was most strongly associated with residential distance to the nearest A2 (primary road without limited access) roadway, even after adjustment for residential distance to the nearest A1 (primary highway with limited access) roadway (see online supplemental table 2).

To further characterise the functional form of the relationship between residential distance to the nearest major roadway and eGFR, we additionally modelled residential distance to the nearest major roadway as a continuous variable using penalised

Table 1 Characteristics of 1103 patients residing in the greater Boston area admitted to the Beth Israel Deaconess Medical Center with confirmed acute ischaemic stroke between 1 April 1999 and 31 December 2004

	Total	Distance of residence to nearest major roadway (m)					
	(n=1103)	0 to ≤50 (n=38)	>50 to ≤100 (n=44)	>100 to ≤200 (n=68)	>200 to ≤400 (n=152)	>400 to ≤1000 (n=259)	>1000 (n=542)
Age (year, mean±SD)	72.9±14.3	74.8±12.4	78.6±12.2	70.7±13.8	73.3±14.8	73.3±14.3	72.3±14.5
Male, n (%)	500 (45.3)	20 (52.6)	20 (45.5)	32 (47.1)	76 (50.0)	111 (42.9)	241 (44.5)
Race, n (%)							
White	696 (63.1)	21 (55.3)	27 (61.4)	44 (64.7)	92 (60.5)	166 (64.1)	346 (63.8)
Black	107 (9.7)	2 (5.3)	3 (6.8)	13 (19.1)	22 (14.5)	24 (9.3)	43 (7.9)
Other	300 (27.2)	15 (39.5)	14 (31.8)	11 (16.2)	38 (25.0)	69 (26.6)	153 (28.2)
Current smoker, n (%)	161 (14.6)	5 (13.2)	1 (2.3)	10 (14.7)	20 (13.2)	44 (17.0)	81 (14.9)
Medical history, n (%)							
Diabetes	325 (29.5)	7 (18.4)	16 (36.4)	25 (36.8)	42 (27.6)	65 (25.1)	170 (31.4)
Hypertension	768 (69.6)	25 (65.8)	26 (59.1)	51 (75.0)	117 (77.0)	178 (68.7)	371 (68.5)
Coronary artery disease	292 (26.5)	7 (18.4)	9 (20.5)	20 (29.4)	44 (29.0)	65 (25.1)	147 (27.1)
Heart failure	137 (12.4)	6 (15.8)	3 (6.8)	6 (8.8)	13 (8.6)	30 (11.6)	79 (14.6)
Medication use, n (%)							
ACEI	407 (36.9)	14 (36.8)	11 (25.0)	25 (36.8)	53 (34.9)	105 (40.5)	199 (36.7)
Aspirin	466 (42.3)	18 (47.4)	18 (40.9)	35 (51.5)	62 (40.8)	112 (43.2)	221 (40.8)
Statins	327 (29.7)	10 (26.3)	14 (31.8)	24 (35.3)	45 (29.6)	68 (26.3)	166 (30.6)
Census variables							
Median household income, $1000, median (IQR)	56.1 (33.3)	61.1 (42.5)	56.4 (37.3)	52.8 (42.1)	47.5 (37.2)	49.9 (32.1)	59.2 (27.8)
Percent of people ≥25 years of age without high school diploma (%, median (IQR))	10.5 (15.9)	6.4 (11.7)	5.8 (9.4)	10.3 (19.0)	14.8 (19.0)	10.6 (16.1)	10.5 (14.8)
eGFR (ml/min/1.73 m^2, mean±SD)	66.4±24.8	60.7±24.7	59.3±24.1	64.2±27.1	66.8±24.8	64.9±23.7	68.2±24.9

ACEI, ACE inhibitor; eGFR, estimated glomerular filtration rate.

splines (figure 3). This analysis confirmed that the functional form of this relationship was approximately log-linear.

The association between distance to major roadway and eGFR did not vary by age, sex, race, diabetes, hypertension or median income in the neighbourhood (all p values ≥0.20 in testing for interaction; see online supplementary table 3).

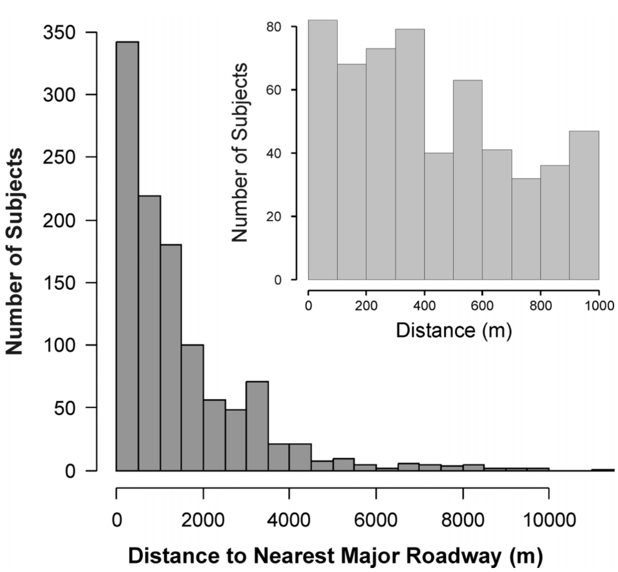

Figure 1 Distribution of residential distance to major roadway among 1103 Boston-area patients admitted to a large tertiary-care medical centre with confirmed acute ischaemic stroke between 1 April 1999 and 31 December 2004. The inset shows the distribution among patients living ≤1 km from the nearest major roadway.

DISCUSSION

In this cohort of patients hospitalised with acute ischaemic stroke, we observed a statistically significant association between residential proximity to major roadway and lower renal function adjusting for patient demographics, medical history and neighbourhood-level indicators of socioeconomic status. Specifically, renal function decreased approximately exponentially with increasing residential proximity to the nearest major

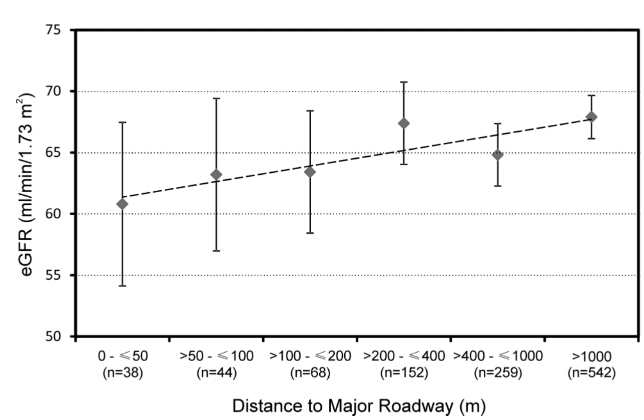

Figure 2 Adjusted mean estimated glomerular filtration rate (and 95% CIs) by distance to major roadway. Adjusted for age, sex, race, smoking status, diabetes, hypertension, heart failure, coronary artery disease, treatment with ACE inhibitor, median household income and percentage of residents without high school diploma.

Table 2 Mean adjusted change in eGFR (95% CI) levels comparing patients living 50 m to patients living 1000 m from the nearest major roadway*

Model	eGFR difference (ml/min/1.73 m^2)†	95% CI	p Value
Unadjusted	−5.7	−9.0 to −2.3	<0.001
Adjusted for age and sex	−3.8	−6.7 to −0.9	0.01
Fully adjusted‡	−3.9	−6.7 to −1.0	0.007

*From a model where the natural logarithm of residential distance to major roadway was entered as a continuous variable.
†A negative value indicates that adjusted mean eGFR is lower among patients living 50 m than patients living 1000 m from a major roadway.
‡Adjusted for age, sex, race, smoking status, diabetes, hypertension, heart failure, coronary artery disease, treatment with ACE inhibitor, median household income and percentage of residents without high school diploma.
eGFR, estimated glomerular filtration rate.

roadway. In a model including the natural log of residential distance to major roadways as a continuous variable, mean eGFR levels among patients living 50 m from a major roadway were 3.9 ml/min/1.73 m^2 (95% CI 1.0 to 6.7) lower than mean levels in patients living 1000 m from a major roadway. To put this result into context, this difference in eGFR is comparable in magnitude to the reduction in eGFR observed for a 4-year increase in age in this cohort or among NHANES III participants.[20] The magnitude of this association did not differ significantly across categories of age, sex, race, history of hypertension, diabetes or socioeconomic status.

There is growing evidence that living near major roadways contributes to the incidence of vascular disease,[3–6 8–10] and adverse prognosis among patients with prevalent cardiovascular disease.[7] Living close to a major roadway is associated with higher levels of exposure to air pollution from traffic[17 18] and an increased risk of stroke and other major adverse

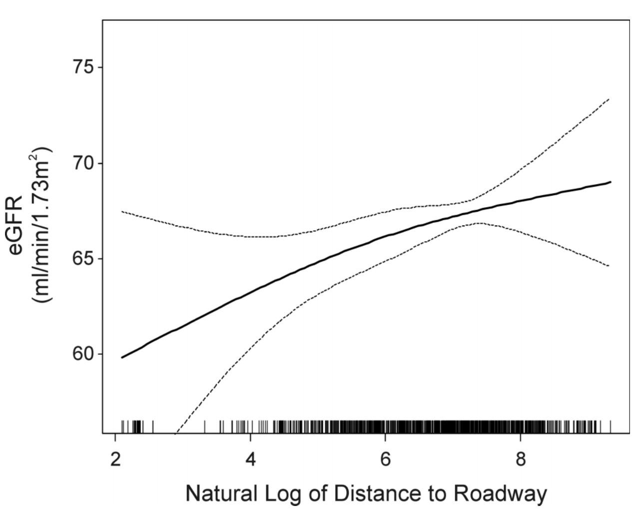

Figure 3 Penalised spline fit showing the estimated glomerular filtration rate (eGFR) as a function of residential distance to nearest major roadway among 1103 patients hospitalised with ischaemic stroke. Data were fitted using a penalised spline with 2 degrees of freedom and adjusted for age, sex, race, smoking status, diabetes, hypertension, heart failure, coronary artery disease, treatment with ACE inhibitor, median household income and percentage of residents without high school diploma. The solid line represents the adjusted mean eGFR and the dashed lines 95% CI bands. The distribution of distance to roadway is displayed by the rug plot along the x-axis.

cardiovascular events including myocardial infarction.[5 6] Long-term exposure to traffic pollution leads to vascular endothelial injury, systemic inflammation, atherosclerosis and microvascular changes.[1 2 21] Evidence from apo-E knockout mice and hyperlipidemic rabbits indicates that long-term exposure to urban air pollution causes increased atherosclerosis with inflammatory characteristics.[22 23] Moreover, in community-dwelling adults, traffic-related pollution is positively associated with carotid intima-media thickness.[24–28] In the Multi Ethnic Study of Atherosclerosis (MESA), living closer to a major roadway was associated with smaller diameter retinal arteriolar vessels suggesting an impact on the microvasculature.[29] On the other hand, long-term exposure to ambient air pollution was not associated with urinary albumin/creatine ratio in MESA, although there was an elevated, but not statistically significant, increase in the risk of microalbuminuria.[30]

Using published estimates of the association between eGFR and mortality in the general population,[31] we estimate that, in this cohort of patients, a reduction in residential distance to major roadway from 1000 to 50 m may be associated with a 4% higher rate of cardiovascular mortality and a 1% higher rate of all-cause mortality (ie, rate ratios of 1.04 and 1.01, respectively). By comparison, an ecological study in England and Wales found that stroke death rates were 7% higher in census regions <200 versus >1000 m away from a major road;[5] in a previous study of early survivors of acute myocardial infarction, we found a 27% and 19% higher rate of all-cause and cardiovascular mortality, respectively, comparing patients living ≤100 vs >1000 m from a major roadway.[7] This comparison suggests that lower renal function can at most only account for a portion of the observed association between residential proximity to major roadways and cardiovascular disease risk.

This study has some limitations. First, although we were able to account for several potential individual and neighbourhood-level confounders, we cannot exclude the possibility of residual confounding by socioeconomic status or unhealthy behaviours. Second, we have data neither on how much time patients spent away from home, nor on residential history or on the duration of residence at the address documented at the time of hospital admission. These sources of exposure misclassification may have biased our results towards the null hypothesis of no association. However, the utility of exposure measures based on home address is supported by the national surveys showing that Americans spend an average of 68% of their time at home.[32] Third, most major roadways in the Boston area carry a combination of truck (diesel) and car (predominantly gasoline) traffic. Diesel and gasoline engine emissions may have different effects on cardiovascular endpoints, including renal function, but we are not able to assess this possibility. Interestingly, eGFR was most strongly associated with residential proximity to A2 roadways (primary road without limited access), which in the Boston area tend to favour local traffic with fewer trucks and moving at lower speeds. Fourth, living closer to a major roadway is associated with higher exposure to noise pollution,[19 33] which may also be associated with higher cardiovascular risk.[34 35] We do not have data on noise pollution in the study area, and therefore cannot evaluate whether the observed associations are due to air pollution, noise or other stressors related to living close to a major roadway. Fifth, all subjects resided in the same metropolitan area, potentially limiting the generalisability of these findings to other geographic areas or patient populations. In particular, our results are not necessarily generalisable to cities with a very different vehicle fleet, fuels or topography. Lastly, we evaluated our hypothesis in a convenience sample of patients presenting to hospital with acute ischaemic stroke. If residential proximity to both a major roadway and impaired renal function is causally associated with stroke incidence, eGFR and roadway proximity may appear conditionally associated among stroke patients even if eGFR and roadway proximity are marginally independent in the whole population (ie, a form of Berkson's bias). However, under assumptions of no effect modification, this source of bias would be expected to lead us to underestimate the association between eGFR and residential distance to roadway.[36]

Despite these limitations, our study has several strengths including a novel hypothesis, the use of the CKD-EPI equation to more accurately estimate GFR over a wide range of values, a large sample size and high-quality clinical data allowing for adjustment for potential confounding by clinical characteristics.

In summary, the current study suggests that living near a major roadway is associated with lower eGFR in a cohort of patients presenting with acute ischaemic stroke. If causal, these results imply that exposures associated with living near a major roadway contribute to reduced renal function, an important risk factor for cardiovascular events. This novel hypothesis needs to be confirmed or refuted within the context of a prospective cohort study.

What is already known about the subject

- Living near major roadways has been associated with vascular injury and increased risk of cardiovascular events. The kidney is a highly vascularised organ susceptible to both large vessel artherosclerotic disease and small vessel dysfunction. Living near a major roadway may also be associated with impaired renal function, but this hypothesis has not been previously evaluated.

What this study adds

- We evaluated this hypothesis in a cohort of patients hospitalised with acute ischaemic stroke and found that living near a major roadway was associated with lower renal function as assessed by the estimated glomerular filtration rate. The magnitude of this association was comparable to the reduction in renal function observed for a 4-year increase in age in population-based studies. If causal, these results imply that exposures associated with living near a major roadway contribute to reduced renal function, an important risk factor for cardiovascular events.

Contributors S-HL, GAW and MAM were involved in study concept and design. S-HL, GAW, EHW, EM and MAM were involved in study conduct and analysis, interpretation of results and critical revision of the manuscript. S-HL and GAW were involved in drafting of the manuscript. GAW and MAM were involved in funding.

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Competing interests None.

Ethics approval Committee on Clinical Investigations, Beth Israel Deaconess Medical Center.

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