Impact of Methylprednisolone on Postoperative Quality of Recovery and Delirium in the Steroids in Cardiac Surgery Trial

A Randomized, Double-blind, Placebo-controlled Substudy

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ABSTRACT

Background: Inflammation after cardiopulmonary bypass may contribute to postoperative delirium and cognitive dysfunction. The authors evaluated the effect of high-dose methylprednisolone to suppress inflammation on the incidence of delirium and postoperative quality of recovery after cardiac surgery.

Methods: Five hundred fifty-five adults from three hospitals enrolled in the randomized, double-blind Steroids in Cardiac Surgery trial were randomly allocated to placebo or 250 mg methylprednisolone at induction and 250 mg methylprednisolone before cardiopulmonary bypass. Each completed the Postoperative Quality of Recovery Scale before surgery and on days 1, 2, and 3 and 1 and 6 months after surgery and the Confusion Assessment Method scale for delirium on days 1, 2, and 3. Recovery was defined as returning to preoperative values or improvement at each time point.

Results: Four hundred eighty-two participants for recovery and 498 participants for delirium were available for analysis. The quality of recovery improved over time but without differences between groups in the primary endpoint of overall recovery (odds ratio range over individual time points for methylprednisolone, 0.39 to 1.45; 95% CI, 0.08–2.04 to 0.40–5.27; $P = 0.943$) or individual recovery domains (all $P > 0.05$). The incidence of delirium was 10% (control) *versus* 8% (methylprednisolone; $P = 0.357$), with no differences in delirium subdomains (all $P > 0.05$). In participants with normal (51%) and low baseline cognition (49%), there were no significant differences favoring methylprednisolone in any domain (all $P > 0.05$). Recovery was worse in patients with postoperative delirium in the cognitive ($P = 0.004$) and physiologic ($P < 0.001$) domains.

Conclusions: High-dose intraoperative methylprednisolone neither reduces delirium nor improves the quality of recovery in high-risk cardiac surgical patients. **(ANESTHESIOLOGY 2017; 126:223-33)**

CARDIAC surgery with cardiopulmonary bypass is common worldwide[1] and is associated with an ubiquitous inflammatory response.[2] This sterile inflammatory response may be associated with adverse outcomes after surgery. Suppressing or modulating the inflammatory response may improve outcomes. High-dose steroids suppress inflammation after cardiopulmonary bypass,[3] but two large randomized controlled trials in cardiac surgery failed to show improvement in mortality or major morbidity,[4,5] postoperative cognitive dysfunction (POCD),[6] delirium,[7] or persistent pain.[8] The largest and most definitive relevant study was the Steroid In caRdiac Surgery (SIRS) trial[5]; the study we present here is a substudy of SIRS.

What We Already Know about This Topic

- Previous studies have demonstrated that the inflammatory response to cardiopulmonary bypass is thought to contribute to postoperative delirium and cognitive dysfunction. Moderate-to-high-dose steroids suppress inflammatory responses.
- This study determined the impact of methylprednisolone on the postoperative quality of recovery and delirium after cardiac surgery using a randomized, double-blind, placebo-controlled model.

What This Article Tells Us That Is New

- High-dose intraoperative methylprednisolone neither reduces delirium nor improves the quality of recovery in high-risk cardiac surgical patients.

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Animal studies have shown associations of cognitive decline with surgical inflammation[9] and anesthesia drugs,[10] and a clinical study has shown differences in early but not late POCD with desflurane *versus* propofol anesthesia.[11] However, there are few data examining the impact of intraoperative high-dose steroids on the postoperative quality of recovery in the days to months after surgery. Further, there are few data identifying whether reduction of inflammation may be of additional benefit in patients with poor presurgery cognition (who could represent a more fragile population) on the incidence of delirium or poor quality of recovery.

Delirium is relatively common after cardiac surgery and is associated with delayed recovery and worse long-term outcomes.[12,13] Both major trials of steroids for cardiac surgery failed to show a difference in the incidence of delirium with steroids (range, 8.0 to 11.7%).[4,5] However, the impact of delirium on multiple domains of recovery over time remains poorly characterized.

Our goal was to determine whether high-dose methylprednisolone improves the quality of postoperative recovery and reduces the incidence of delirium after cardiac surgery involving cardiopulmonary bypass. Specifically, we tested the primary hypothesis that high-dose methylprednisolone improves the quality of recovery compared to placebo. Secondarily, we tested the hypothesis that high-dose methylprednisolone reduces the incidence of delirium during the initial three postoperative days.

Materials and Methods

Three centers participated in this substudy of the SIRS trial (ClinicalTrials.gov identifier: NCT00427388): the Royal Melbourne Hospital (Melbourne, Victoria, Australia), the Cleveland Clinic (Cleveland, Ohio), and the Hamilton Health Sciences Center at McMaster University (Hamilton, Ontario, Canada). Written and informed consent was obtained from participants for the substudy. We evaluated the quality of recovery and delirium without altering the underlying SIRS study. Detailed description of the SIRS design including participants, intervention, randomization, blinding, and allocation has been previously published.[5] Briefly, the SIRS study was a double-blinded, placebo-controlled, multicenter, randomized controlled trial. The intervention was 250 mg methylprednisolone given at anesthetic induction and again just before starting cardiopulmonary bypass. Amendments to the SIRS ethics approvals and local governance approvals were obtained at each center participating in this substudy.

Participants and Settings for the Substudy

Participants were included if they were enrolled in the SIRS study and could speak sufficient English to complete the Postoperative Quality of Recovery Scale (PostopQRS)[14] and did not have known cognitive impairment or psychiatric illness. Inclusion criteria for the SIRS study included age more than 18 yr, European System for Cardiac Risk Evaluation (EuroSCORE) more than or equal to 6, and being able to provide written consent.

Outcomes

Our primary outcome was the quality of recovery over a 6-month period, measured using PostopQRS. The secondary outcomes included the cumulative incidence of delirium measured using the Confusion Assessment Method Intensive Care Unit (CAM ICU) scale,[15] quality of recovery in individual recovery domains, and subdomains of the CAM ICU.

Postoperative Quality of Recovery Measurement

The PostopQRS[14] was used to measure the quality of recovery after surgery. Details of the construct and validation of the PostopQRS have been previously published.[14,16–18] In brief, the quality of recovery is measured using a verbal survey tool that assesses recovery in multiple domains (physiologic, emotive, nociceptive, functional [activity of daily living {ADL}], and cognitive).

Baseline measurements are acquired before surgery. Recovery is a dichotomized outcome defined by a return to at least baseline values or better at each of the postoperative measurement time points. Overall recovery requires recovery in all domains being assessed, and failure in any domain results in failure of overall recovery. The tool is designed for repeated measurements and can be administered either face to face or *via* the telephone.[16]

A description of the items within each domain is shown in table 1. The physiologic domain is assessed whilst the participant is in hospital (days 1 to 3 in this study) and consists of seven items applicable to the postemergence period. The nociceptive domain consists of pain and nausea subscales, the emotive domain consists of depression and anxiety subscales, and the ADL domain consists of four activities of daily living (ability to stand, dress, eat, and walk). The cognitive domain consists of five verbal tests, and domain recovery requires recovery in all five tests. Variance in cognitive performance is a normal event, and accordingly, the definition of recovery in cognitive tests was modified to include a tolerance factor to account for normal variability.[16] Participants are allowed to perform a little worse than their baseline performance and still be scored as recovered, so that recovery = score − (baseline score − tolerance factor) for each question. Participants with baseline cognitive scores that are equal to or less than the tolerance factor are not included in the cognitive domain at subsequent time points as the scoring rules would automatically score them as recovered. Therefore, to be included in the cognitive domain, participants must score at least 1 more than the tolerance factor for each question of the domain (table 1). Further, they are excluded from scoring overall recovery as they cannot be evaluated in the cognitive domain. However, the caveat is that if they fail in any other domain, then they will be scored

Table 1. Description of Recovery Domains Used in the Postoperative Quality of Recovery Scale

Domain	Recovery Parameters Measured	Comment
Physiology	Systolic blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation constitute physiologic recovery. Airway control, level of agitation, level of consciousness, and activity on command relate to emergence and airway safety.	This domain is tested in the immediate and early period. It is principally designed to assess physiologic safety and home readiness for day stay surgery but can be used to track physiologic recovery whilst in hospital for major surgery.
Nociceptive	Patient assessment of pain and nausea at the time of testing	1–5 Likert rating scale using a faces pictorial display to aid ease of response
Emotional	Patient assessment of feelings of anxiety and depression at the time of measurement	Scoring as for nociceptive domain
Activities of daily living	Assesses physical return to normalcy through activities of daily living. Ability to stand, walk, and dress without assistance and ability to eat and drink.	Scored as 3—easily, 2—with difficulty, and 1—not at all.
Cognitive	Five tests to assess orientation, verbal memory, executive functioning, attention, and concentration. (1) Orientation—no tolerance factor (2) Digits forward—tolerance factor = 2 (3) Digits back—tolerance factor = 1 (4) Word recall—tolerance factor = 3 (5) Word generation—tolerance factor = 3	Tests produce performance scores. The tests are derived from validated and extensively used neurocognitive tests. Performance variability tolerance factor is applied. Participants not included in subsequent analysis if baseline scores are equal to or less than the tolerance factor.

as failed in overall recovery. That is, failure in any domain results in failure in all domains. These participants are not excluded from other recovery domains. The incidence of low baseline scores differs among populations, ranging from near 0 in young volunteers,[16] to 5 to 15% in orthopedic,[18] and around 25 to 35% in cardiac surgery (C. Royse, M.B.B.S., M.D., unpublished data—audit data, 2013 to 2015).

The PostopQRS was conducted within 2 weeks before surgery, at 1, 2, and 3 days after surgery, and 1 and 6 months after surgery. The physiologic domain was only measured on days 1 to 3. Overall recovery is defined as recovery in all of the domains that are measured at each time point, so that overall recovery assessment does not include the physiologic domain after day 3.

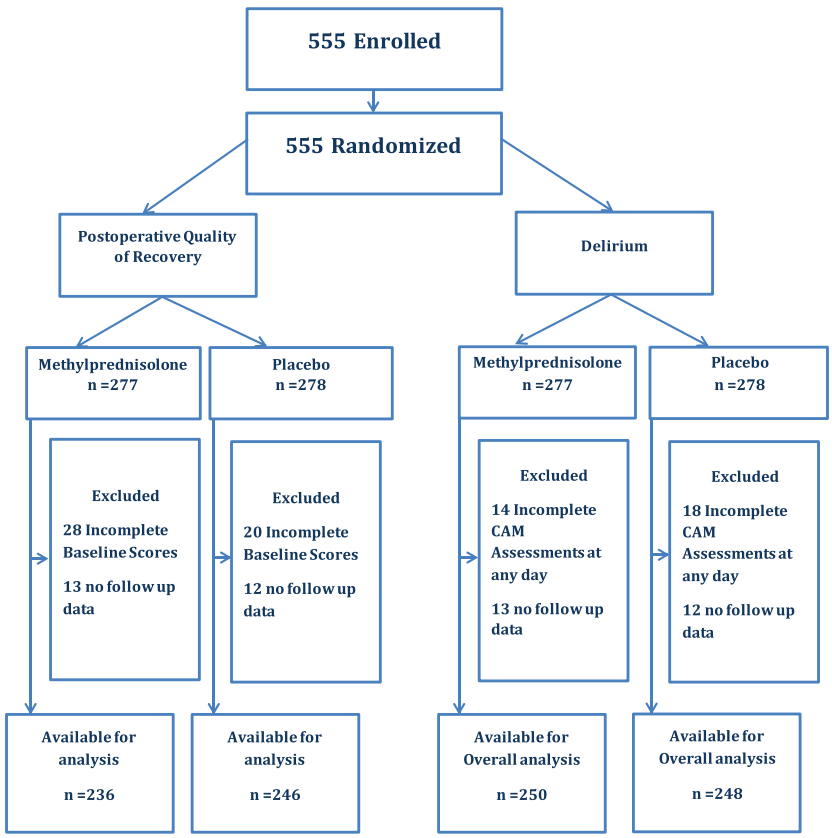

Fig. 1. Participant flowchart. CAM = Confusion Assessment Method.

Table 2. Demographic Data for Participants

	Methylprednisolone (n = 236) n (%)	Placebo (n = 246) n (%)
Age		
Mean (SD), yr	73.4 (10.5)	74.3 (9.3)
< 65	38 (16)	38 (15)
65–80	137 (58)	134 (54)
> 80	61 (26)	74 (30)
Sex		
Male	147 (63)	162 (66)
Female	89 (37)	84 (34)
Body mass index, mean (SD)	28.7 (5.7)	28.7 (5.1)
Coexisting medical conditions		
Angina	90 (38)	101 (41)
Congestive heart failure	75 (29)	63 (26)
Previous myocardial infarction	70 (30)	76 (31)
Atrial fibrillation	52 (22)	76 (31)
Previous cardiac surgery	42 (18)	51 (21)
Previous stroke	23 (10)	13 (5)
Diabetes	75 (32)	69 (28)
Hypertension	192 (81)	207 (84)
Dyslipidemia	175 (74)	177 (72)
Peptic ulcer disease	6 (3)	4 (2)
Previous gastrointestinal hemorrhage	4 (2)	8 (3)
Peripheral artery disease	40 (17)	41 (17)
Chronic renal failure	22 (9)	16 (7)
Dialysis	3 (> 1)	4 (> 1)
Chronic obstructive pulmonary disease	36 (15)	42 (17)
Current smoker	29 (12)	32 (13)
Former smoker	114 (48)	129 (52)
Cardiac status		
Coronary artery stenosis > 50%	24 (11)	25 (11)
Left main circumflex	96 (44)	98 (44)
Left anterior descending	107 (49)	116 (52)
Right coronary	100 (46)	104 (46)
Surgery type		
Valve surgery	111 (47)	126 (53)
CABG on pump	59 (50)	58 (50)
CABG + valve surgery	47 (50)	47 (50)
Aortic surgery	19 (56)	15 (44)
Tricuspid stenosis*	1 (< 1)	1 (< 1)
Mitral stenosis*	31 (17)	29 (15)
Aortic stenosis*	112 (57)	125 (60)
Tricuspid regurgitation*	114 (60)	97 (50)
Aortic regurgitation*	128 (67)	134 (68)
Mitral regurgitation*	92 (50)	99 (51)
Aortic aneurysm*	34 (14)	36 (15)
Ventricular aneurysm*	1 (< 1)	3 (1)
Preoperative medications		
ACE inhibitors	112 (47)	109 (44)
ARB agent	49 (21)	53 (22)
β blockers	149 (63)	142 (58)
Calcium channel blocker	84 (36)	77 (31)
Diuretics	100 (41)	120 (51)
Insulin	24 (10)	21 (9)
Antiarrhythmic	7 (3)	16 (7)
Digoxin	11 (5)	14 (5)
Nitroglycerine	65 (28)	64 (26)
Statin	182 (77)	184 (75)
Lipid-lowering agent	18 (8)	18 (7)
Oral hypoglycemic agent	42 (18)	43 (17)
H_2 antagonist	10 (4)	20 (8)
Proton pump inhibitor	83 (35)	71 (29)
Aspirin	129 (55)	139 (57)
Thienopyridine	44 (19)	40 (16)
Vitamin K antagonist	21 (9)	25 (10)
Dabigatran	5 (2)	3 (1)
Low baseline PostopQRS cognitive domain scores	109 (46)	125 (51)

*Uncorrected valvular disease of any grade that was reported.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft surgery; H2 = histamine type 2 receptor; PostopQRS = the Postoperative Quality of Recovery Scale.

Delirium

Delirium was measured for all patients in the morning of days 1 to 3 after surgery using the CAM ICU[15] and scored according to the published criteria. Patients in whom the CAM ICU had not been performed on all 3 days were included if CAM ICU had been completed on at least one of the 3 days. The Richmond Agitation and Sedation Scale[19] evaluates the sedation level in every patient before the CAM ICU assessment. Patients with a Richmond Agitation and Sedation Scale score of −4 or −5 were excluded from further evaluations.

Sample Size

Three centers participated in this substudy of SIRS, and each included as many patients as practical. For the postoperative quality of recovery, we estimated sample size from the PostopQRS validation study.[14] We used a Cochran–Mantel–Haenszel design for multiple measurements up to 3 months and a two-sided difference with 80% power at the 0.05 significance level. For an effect size of odds ratio (OR) of 2.0, 225 participants in each group were required.

Statistical Methods

Participants were excluded *post hoc* from quality of recovery analysis if they had incomplete baseline data. Participants with low baseline cognitive scores were excluded from cognitive analysis and from overall recovery (unless they failed to recover in a different domain). Participants were excluded from delirium analysis if they had insufficient data to be able to score the CAM ICU at all time points but were included if there was at least 1 time point with complete CAM ICU data. We considered patients to have experienced postoperative delirium when CAM ICU testing scored positive at any one assessment.[20]

Differences in the quality of recovery between groups over time were assessed using the Cochrane-Mantel-Haenszel test.

The incidence of delirium was assessed using Fisher exact test. $P < 0.05$ defined significance. A Bonferroni correction would be used if the difference between groups for either primary outcome was $P < 0.05$. Analysis was performed using SPPS version 22 (IBM, USA). For secondary outcomes, $P < 0.01$ was used to define significance in order to reduce the risk of type I error due to multiple analyses or for subgroup interactions.

Two subanalyses were conducted. First, we analyzed whether participants who suffered delirium had poorer quality of recovery, which was a planned analysis. The second, which was decided *post hoc* due to the high incidence of low cognitive baseline scores in this cohort of patients, was to examine whether participants with low baseline cognitive scores recovered more slowly or suffered more delirium than participants with normal cognitive baseline scores.

Results

Five hundred and fifty-five participants were enrolled into the substudy. The participant flowchart is shown in figure 1 for both the PostopQRS and delirium analyses. Participants were excluded from analysis for the PostopQRS if they had incomplete baseline data (methylprednisolone, 28; control, 20) or no postsurgery data (methylprednisolone, 13; control, 12). Participants were excluded from analysis for delirium if they had no complete CAM ICU data on any day (methylprednisolone, 14; control, 18) or no CAM ICU data on any day (methylprednisolone, 13; control, 12). The preoperative and operative data for both groups are shown in table 2.

The overall quality of recovery and domain level recovery for all included participants are shown in figure 2. Recovery improved over time, but steroids did not alter the primary endpoint of overall recovery ($P = 0.943$) nor any of the individual recovery domains (all $P > 0.05$). The incidence of delirium for the control group was 10%, which was similar to that in patients given methylprednisolone (8%; OR, 0.74; 95% CI, 0.40 to 1.37; $P = 0.357$; table 3). There were also no differences in any of the delirium domains (all $P > 0.05$).

The quality of recovery for participants with low *versus* normal or high cognitive baseline scores is shown in

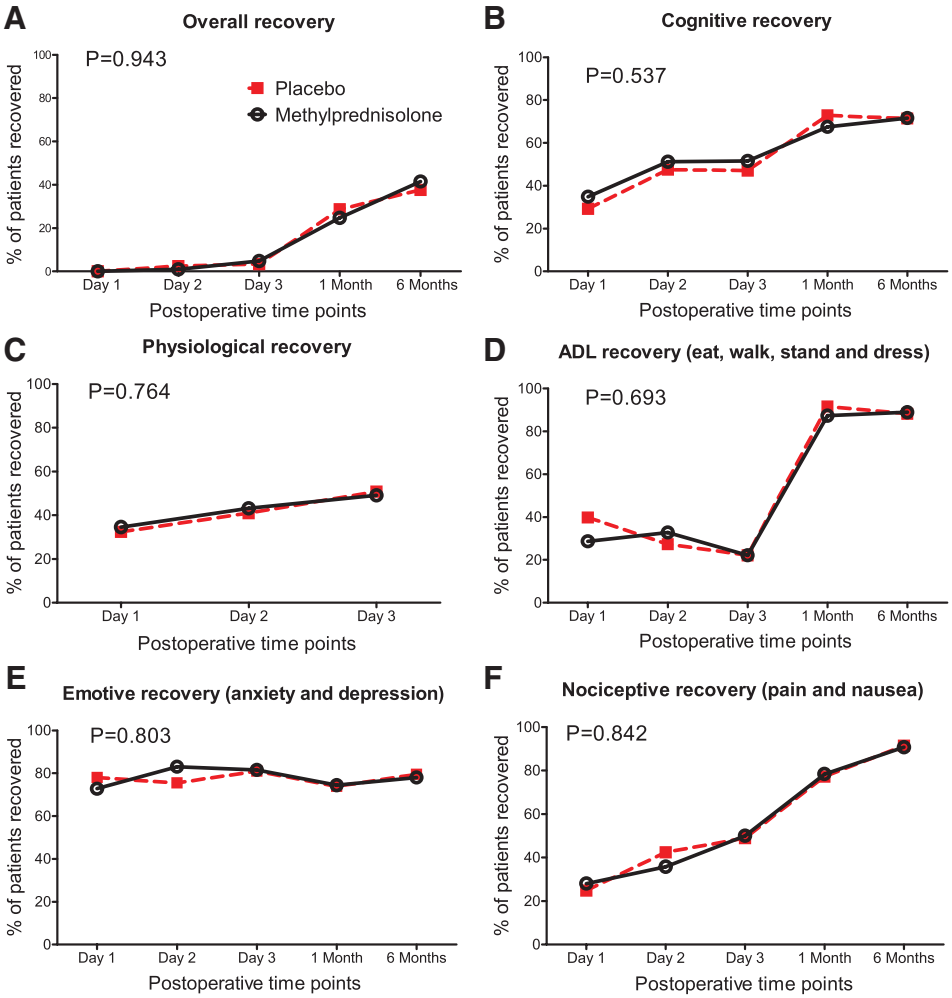

Fig. 2. Postoperative quality of recovery for all participants comparing placebo and methylprednisolone groups. Overall recovery (*A*), cognitive domain (*B*), physiologic recovery (*C*), activities of daily living (ADL; *D*), emotive recovery (*E*), and nociceptive recovery (*F*).

Table 3. Incidence of Delirium and Confusion Assessment Method Intensive Care Unit Subscales

Delirium	Methylprednisolone (n = 250) n (%)	Placebo (n = 248) n (%)	*P* Value
Delirium	20 (8)	26 (10)	0.357
Fluctuation of mental status	91 (36)	106 (43)	0.169
Inattention	38 (15)	45 (18)	0.402
Altered consciousness	90 (36)	107 (43)	0.119
Disorganized thinking	14 (6)	22 (9)	0.170
Low baseline score patients	Methylprednisolone (n = 109)	Placebo (n = 112)	
Delirium	8 (7)	16 (14)	0.130
Fluctuation of mental status	42 (39)	54 (48)	0.175
Inattention	18 (17)	32 (29)	0.037
Altered consciousness	40 (37)	52 (46)	0.172
Disorganized thinking	9 (8)	14 (13)	0.380
Normal baseline score patients	Methylprednisolone (n = 122)	Placebo (n = 116)	
Delirium	7 (6)	10 (9)	0.455
Fluctuation of mental status	38 (31)	45 (39)	0.224
Inattention	14 (12)	11 (10)	0.676
Altered consciousness	39 (32)	48 (41)	0.141
Disorganized thinking	4 (3)	6 (5)	0.531
All patients	Low baseline (n = 221)	Normal baseline (n = 238)	
Delirium	24 (11)	17 (7)	0.191
Fluctuation of mental status	96 (43)	83 (35)	0.069
Inattention	50 (23)	25 (11)	0.001
Altered consciousness	92 (42)	87 (37)	0.292
Disorganized thinking	23 (10)	10 (4)	0.011

Delirium is the incidence of delirium at any time during the first 3 days after surgery. Fluctuation of mental status, inattention, altered consciousness, and disorganized thinking are subdomains of the Confusion Assessment Method Intensive Care Unit scale.

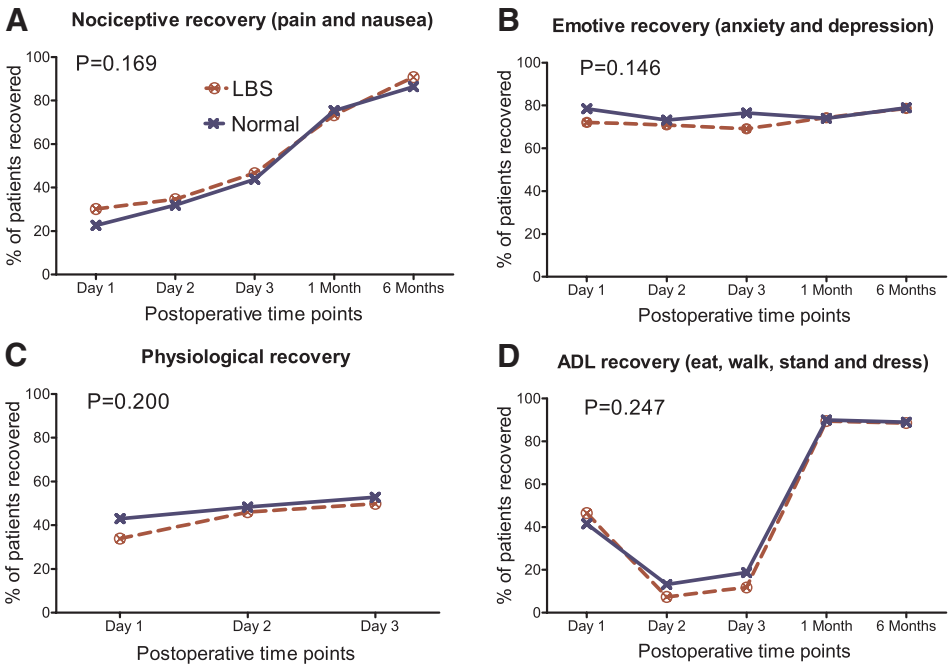

Fig. 3. Postoperative quality of recovery for all participants comparing low baseline cognitive scores (LBS) *versus* normal baseline cognitive scores (normal). Nociceptive recovery (*A*), emotive recovery (*B*), physiologic recovery (*C*), and activities of daily living (ADL; *D*).

figure 3. There were no significant differences in recovery domains (all $P > 0.05$). A comparison of groups for those with low baseline scores is shown in figure 4, showing no difference in the recovery domains. A comparison of groups for participants with normal cognitive baseline scores is shown in figure 5. There were no differences in overall recovery or any individual recovery domain (all $P > 0.05$).

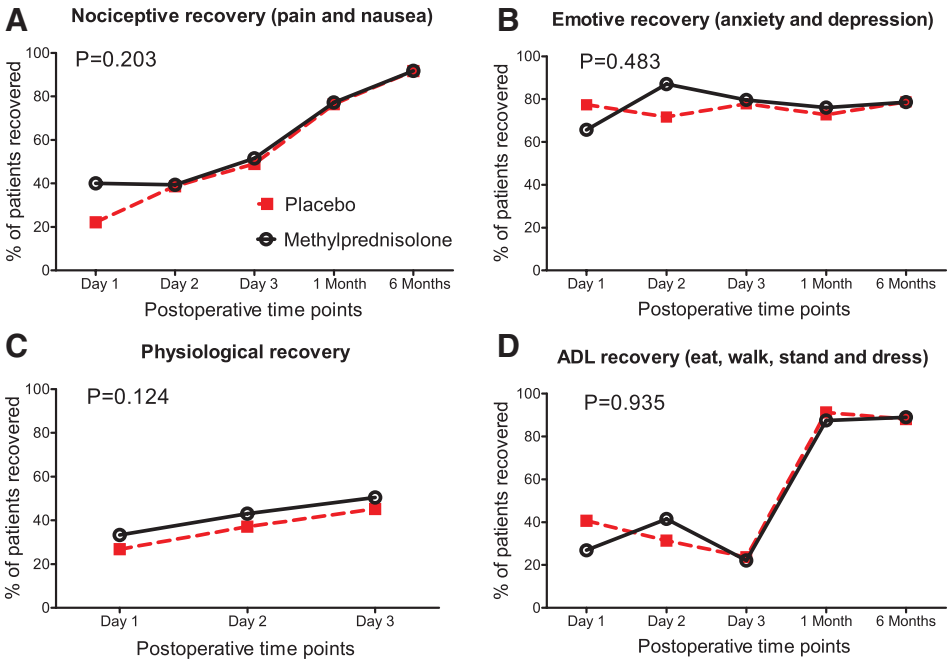

Fig. 4. Postoperative quality of recovery for participants with low baseline cognitive scores, comparing placebo and methylprednisolone groups. Nociceptive recovery (*A*), emotive recovery (*B*), physiologic recovery (*C*), and activities of daily living (ADL; *D*).

The incidence of delirium for participants with low baseline cognitive scores was 11% *versus* 7% in patients with normal baseline scores (OR, 0.63; 95% CI, 0.33 to 1.21; $P = 1.91$). The incidence of delirium for each group and for the CAM ICU components is shown in table 3. There was no difference in the incidence of delirium or of CAM ICU components between groups. Participants with low baseline cognitive scores had a higher incidence of inattention (23% *vs.* 11%; $P = 0.001$) but not more disorganized thinking (10% *vs.* 4%; $P = 0.011$). In patients with normal baseline cognitive scores, there were no significant differences between the methylprednisolone and control groups in delirium (7% *vs.* 10%; OR, 0.51; 95% CI, 0.57 to 4.22; $P = 0.455$) or components. For patients with low baseline cognitive scores, the incidence of delirium was 7% in the methylprednisolone group *versus* 14% in the control group (OR, 0.456; 95% CI, 0.86 to 5.14; $P = 0.13$). There were no significant differences in the incidence of inattention (17% *vs.* 29%; $P = 0.037$) on the CAM ICU scale.

The comparison of the quality of recovery for participants with and without delirium is shown in figure 6. Participants suffering delirium in the first 3 days after surgery had similar recovery at 6 months although not significantly so. Poorer recovery occurred in the cognitive domain ($P = 0.004$) and physiologic domain ($P < 0.001$) but not in the other recovery domains.

The effect size expressed as OR with 95% CIs for the above comparisons is shown in table 4 for each measurement and at each time point.

Discussion

Intraoperative high-dose methylprednisolone before cardiopulmonary bypass did not improve the postoperative quality of recovery nor did steroids reduce the incidence of delirium. These findings are consistent with the SIRS and Dexamethasone for Cardiac Surgery (DECS) studies that showed that high-dose steroids did not improve mortality, morbidity, delirium, POCD, or persistent pain.[4–8]

The effect of steroids on delirium on day 3 after surgery was evaluated in the DECS trial, with delirium defined by the need for treatment with postoperative neuroleptic drugs.[4] Delirium was similar in patients given dexamethasone (9.2% *vs.* 11.7%; $P = 0.06$). In a substudy of 768 patients in whom delirium was measured over 4 days with the CAM ICU, the incidence of delirium and the duration did not differ between the groups (dexamethasone, 14.2% *vs.* 14.9%; adjusted OR, 0.85; 95% CI, 0.55 to 1.31; mean duration [interquartile range], 2 [1 to 3] *vs.* 2 [1 to 2] days, respectively; $P = 0.45$).[7] In the SIRS study, the incidence of delirium on day 3 was 8% in both groups ($P = 0.80$). The incidence of delirium in our substudy is consistent with the DECS trial as was the lack of steroid efficacy.

Subanalysis of Patients with Low Baseline Cognitive Scores

Participants in the SIRS trial all had a EuroSCORE I of 6 or greater, and thus, all had considerable comorbidities and/or were scheduled for especially major surgery. The incidence of low baseline scores approaches 0 in young volunteers,[16] 5 to 15% in orthopedic surgery,[18] and approximately 25 to 35% in the general cardiac surgery population (C. Royse, M.B.B.S., M.D., unpublished data—audit data, 2013 to 2015). In our current cohort, almost half of the patients had low baseline scores, indicating that baseline cognition was

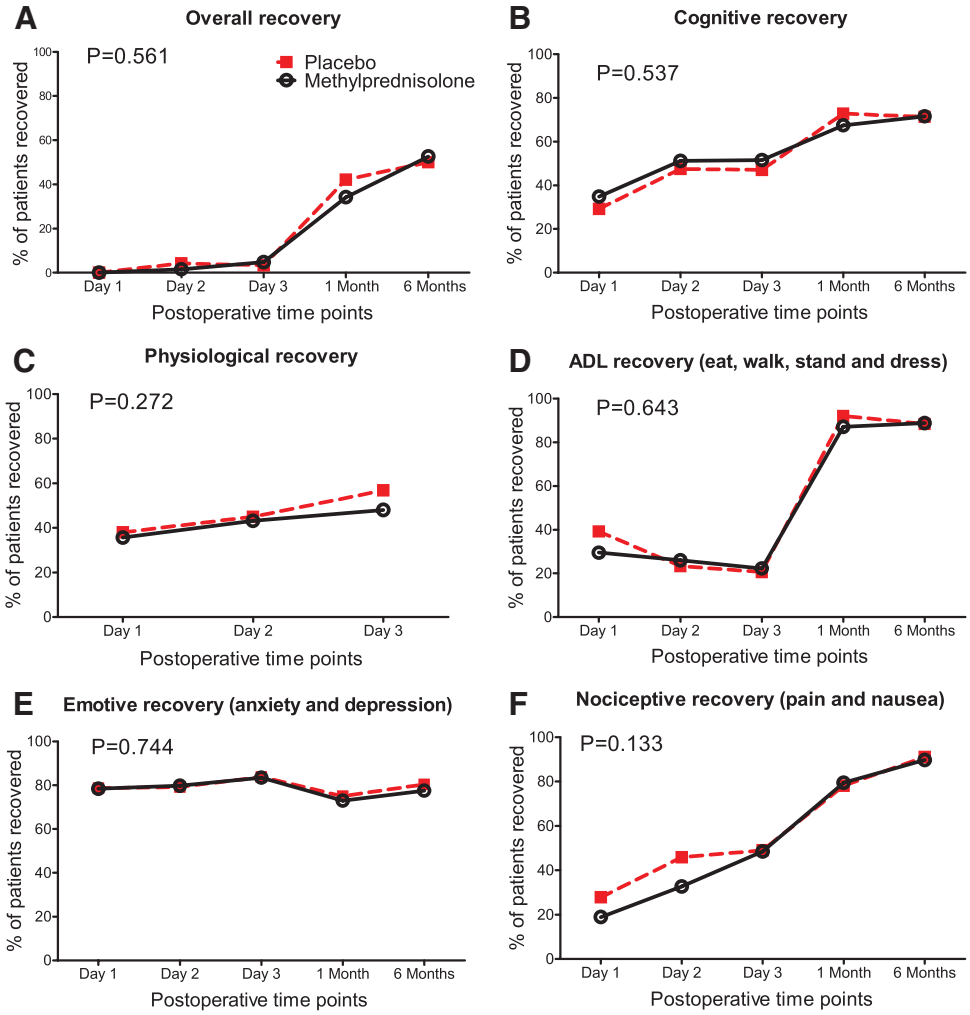

Fig. 5. Postoperative quality of recovery for participants with normal baseline cognitive scores, comparing placebo and methylprednisolone groups. Overall recovery (*A*), cognitive domain (*B*), physiologic recovery (*C*), activities of daily living (ADL; *D*), emotive recovery (*E*), and nociceptive recovery (*F*).

poor. It is possible that these patients were frail and generally unwell, and poor cognition is part of that medical state (cognitive frailty). Thus, they were more likely to suffer delirium or poor recovery in other domains. A theoretical consideration is that steroids might especially benefit such patients; however, there was no evidence that methylprednisolone was effective in this cohort. Our data do not support high-dose methylprednisolone in cognitively frail patients.

The concept of cognitive frailty and poor postoperative outcomes was explored by Silbert *et al.*[21,22] Using a seven-component neuropsychologic test battery, they compared a cohort of patients undergoing coronary artery surgery against nonoperative controls to identify the incidence of baseline cognitive impairment. The cardiac surgery group performed worse than controls on all tests other than the Grooved Pegboard test. The incidence of baseline cognitive impairment, defined by impairment in more than or equal to two of seven tests compared to nonoperative controls, was 35%, which is consistent with our finding of a high proportion of patients with low baseline cognitive scores. In a study of patients having hip arthroplasty, Silbert *et al.*[21] identified baseline cognitive impairment in 32% of patients. In their cohort, there was an increased incidence of POCD and cognitive decline compared to those with normal cognition preoperatively. Oldham *et al.*[23] assessed cognitive and functional status preoperatively and showed association with cognitive impairment after coronary artery surgery. Our study did not specifically investigate cognitive decline or dementia, and we, therefore, cannot determine whether patients with low baseline cognitive scores had a greater risk of developing postoperative dementia.

Subanalysis of the Impact of Delirium on the Quality of Recovery

Our second subanalysis was to identify the effect of delirium on the quality of recovery after surgery. Participants with delirium had worse overall quality of recovery, most evident at 6 months after surgery, although not statistically so. Within individual

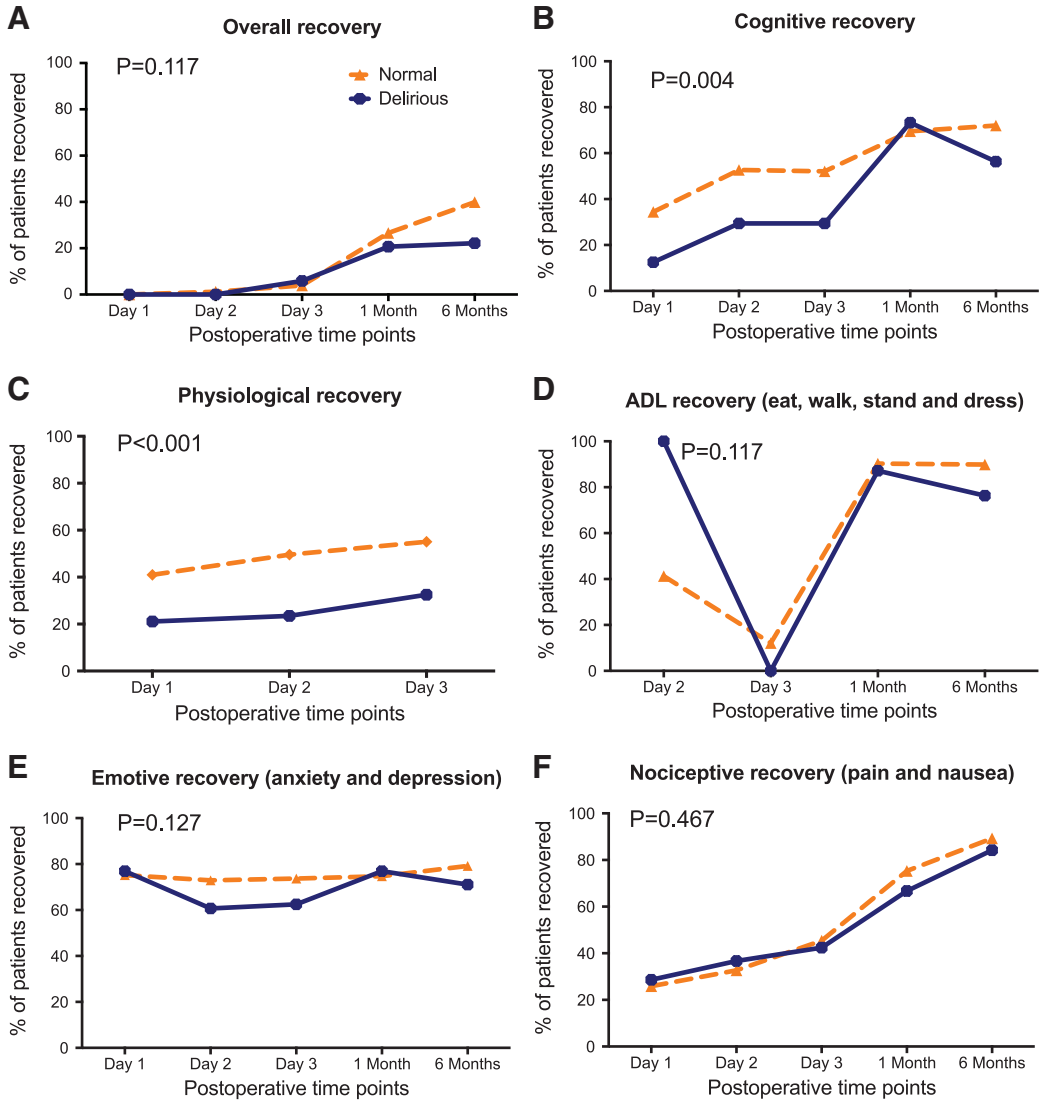

Fig. 6. Postoperative quality of recovery for participants comparing delirious participants *versus* no delirium (normal). Overall recovery (*A*), cognitive domain (*B*), physiologic recovery (*C*), activities of daily living (ADL; *D*), emotive recovery (*E*), and nociceptive recovery (*F*).

domains, cognitive recovery and physiologic recovery were worse. Our results are consistent with other studies showing worse long-term clinical outcomes in participants who develop delirium. Brown *et al.*[24] showed that delirium after cardiac surgical procedures was independently associated with increased intensive care length of stay and greater hospital charges. Mangusan *et al.*[12] found that patients with delirium after cardiac surgery stayed longer in the hospital, suffered more falls, and were more likely to be discharged to a nursing facility or need home medical services. In a prospective, observational, follow-up study 1 to 1.5 yr after surgery, Koster *et al.*[13] showed that patients with delirium after cardiac surgery had higher mortality, more readmissions to hospital, and poorer cognitive and functional outcomes. There is, thus, a strong consensus that patients with delirium do worse in many respects.

Although our study is large, it is not large enough to provide robust power, especially for identifying subgroups that could be clinically important. For example, it would have been interesting to evaluate a subset of especially frail patients. Approximately 15% of participants were excluded after randomization because of incomplete or missing data, with roughly comparable numbers excluded in each randomized group. CAM ICU testing was performed in the morning and only once a day, for logistic reasons. More frequent assessments might capture a higher incidence of delirium but potentially increase the risk of test fatigue and refusal to participate, especially in predelirious patients. We previously observed this attrition bias with patients experiencing postoperative delirium being more likely to refuse delirium assessment.[25] We did not record the use of major tranquillizers or other medications used to treat delirium nor any medical interventions, which may affect the incidence of delirium. Six months is a reasonable follow-up period; however, it remains possible that further recovery occurs

Table 4. ORs and 95% CIs for Quality of Recovery and Delirium in Patients Undergoing Cardiac Surgery

Postoperative Time Points	Overall Recovery	Cognitive Recovery	Physiologic Recovery	Nociceptive Recovery	Emotive Recovery	ADL Recovery
Superiority in recovery of methylprednisolone patients compared to placebo, OR (95% CI)						
1 d	—	1.30 (0.76–2.23)	1.11 (0.76–1.62)	1.17 (0.72–1.92)	0.75 (0.45–1.26)	0.61 (0.32–1.16)
2 d	0.39 (0.08–2.04)	1.16 (0.70–1.91)	1.09 (0.76–1.57)	0.76 (0.50–1.14)	1.59 (0.97–2.61)	1.30 (0.83–2.04)
3 d	1.45 (0.40–5.27)	1.20 (0.73–1.99)	0.93 (0.65–1.34)	1.04 (0.70–1.14)	1.04 (0.63–1.74)	1.01 (0.62–1.63)
1 mo	0.82 (0.50–1.34)	0.78 (0.44–1.37)	—	1.07 (0.68–1.68)	1.03 (0.67–1.58)	0.63 (0.34–1.16)
6 mo	1.18 (0.74–1.88)	1.01 (0.57–1.79)	—	0.92 (0.47–1.77)	0.91 (0.58–1.45)	1.07 (0.59–1.92)
Superiority in recovery of normal cognitive baseline score patients compared to low baseline score patients, OR (95% CI)						
1 d	—	—	1.37 (0.93–2.01)	0.70 (0.43–1.15)	1.40 (0.85–2.37)	0.98 (0.50–1.90)
2 d	—	—	1.19 (0.83–1.71)	1.00 (0.66–1.49)	1.01 (0.62–1.65)	0.58 (0.37–0.91)
3 d	—	—	1.20 (0.84–1.72)	0.94 (0.63–1.4)	1.38 (0.83–2.31)	0.92 (0.57–1.49)
1 mo	—	—	—	1.12 (0.72–1.76)	0.99 (0.64–1.51)	1.02 (0.56–1.86)
6 mo	—	—	—	0.84 (0.43–1.63)	1.02 (0.64–1.62)	1.01 (0.56–1.82)
Superiority in recovery of methylprednisolone treatment compared to placebo in low cognitive baseline score patients, OR (95% CI)						
1 d	—	—	1.36 (0.78–2.4)	2.35 (1.17–4.73)	0.56 (0.28–1.14)	0.54 (0.18–1.65)
2 d	—	—	1.29 (0.76–2.17)	1.03 (0.57–1.85)	2.63 (1.23–5.60)	1.55 (0.82–2.91)
3 d	—	—	1.24 (0.74–2.07)	1.11 (0.63–1.97)	1.11 (0.55–2.24)	0.92 (0.46–1.81)
1 mo	—	—	—	1.05 (0.55–1.99)	1.19 (0.64–2.21)	0.68 (0.28–1.62)
6 mo	—	—	—	1.02 (0.38–2.76)	0.99 (0.51–1.93)	1.10 (0.47–2.57)
Superiority in recovery of methylprednisolone treatment compared to placebo in normal cognitive baseline score patients, OR (95% CI)						
1 d	—	1.30 (0.76–2.23)	0.91 (0.54–1.52)	0.6 (0.29–1.24)	0.98 (0.47–2.09)	0.65 (0.30–1.42)
2 d	0.37 (0.07–1.97)	1.16 (0.70–1.91)	0.93 (0.56–1.54)	0.58 (0.33–1.01)	1.04 (0.53–2.05)	1.15 (0.60–2.22)
3 d	1.45 (0.40–5.27)	1.20 (0.73–1.99)	0.70 (0.42–1.17)	0.98 (0.57–1.7)	0.98 (0.46–2.06)	1.11 (0.56–2.18)
1 mo	0.71 (0.42–1.22)	0.78 (0.44–1.37)	—	1.09 (0.58–2.05)	0.90 (0.50–1.64)	0.58 (0.24–1.38)
6 mo	1.11 (0.66–1.86)	1.01 (0.57–1.79)	—	0.85 (0.35–2.05)	0.85 (0.45–1.60)	1.04 (0.46–2.35)
Superiority in recovery of non-delirious patients to delirious patients, OR (95% CI)						
1 d	—	3.67 (0.81–16.57)	4.26 (1.64–11.08)	0.88 (0.27–2.89)	0.91 (0.24–3.40)	—
2 d	—	2.68 (0.91–7.85)	3.52 (1.59–7.80)	0.70 (0.33–1.48)	2.84 (1.31–6.18)	2.64 (0.89–7.82)
3 d	0.69 (0.08–5.78)	2.61 (0.89–7.65)	2.50 (1.26–4.97)	1.19 (0.58–2.44)	2.75 (1.29–5.89)	1.64 (0.60–4.46)
1 mo	1.12 (0.46–2.73)	0.83 (0.25–2.70)	—	0.91 (0.40–2.04)	0.88 (0.41–1.93)	1.33 (0.49–3.61)
6 mo	1.97 (0.81–4.83)	2.00 (0.71–5.62)	—	1.25 (0.42–3.74)	1.55 (0.74–3.25)	2.69 (1.19–6.09)

Data are reported as ORs with CIs for methylprednisolone being superior to placebo, *i.e.*, an OR of more than 1 indicates superiority of methylprednisolone, whereas an OR of less than 1 indicates superiority of placebo. ADL: OR cannot be calculated due to the number of patients being either recovered or nonrecovered in either of the groups. Physiological: OR cannot be calculated due to the number of patients being assessed in either of the groups. Overall and cognitive: OR cannot be calculated for unassessable patients due to baseline scoring requirements of the Postoperative Quality of Recovery Scale.
ADL = activity of daily living; OR = odds ratio.

between 6 and 12 months—although it seems unlikely that recovery so long after surgery would differ in the treatment groups. Postdischarge follow-up occurred *via* the telephone, but the telephone use of PostopQRS evaluations has been validated.[16] No attempt was made to assess the impact of site heterogeneity or to make adjustments for site effects.

In summary, high-dose methylprednisolone did not reduce delirium nor improve the quality of recovery in a high-risk cohort of patients recovering from cardiac surgery. Previous work indicates that steroid administration also does not improve other major outcomes in cardiac surgical patients, and patients having cardiac surgery should not routinely be given steroids.

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Competing Interests

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Reproducible Science

Full protocol available from Dr. Whitlock: richard.whitlock@phri.ca. Raw data available from Dr. Whitlock: richard.whitlock@phri.ca.

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