Article title: **Breaking up sedentary time with seated upper body activity can regulate metabolic health in obese high risk adults:
A randomised crossover trial**

Brief title: Seated activity breaks and metabolic health

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ABSTRACT

Aims: To investigate the impact of performing short bouts of seated upper body activity on postprandial blood glucose and insulin levels during prolonged sitting.

Materials and methods: Participants undertook two 7.5 hour experimental conditions in a randomised order: 1) prolonged sitting only 2) sitting interspersed with 5 minutes of seated arm ergometry every 30 minutes. Blood samples were obtained while fasting and throughout the postprandial period following ingestion of two standardised meals.

Incremental Area Under the Curve (iAUC) was calculated for glucose and insulin throughout each experimental condition. Paired samples t-test assessed the difference in iAUC data between conditions for glucose (primary outcome) and insulin (secondary outcome).

Results: Thirteen obese adults (7 female; 6 male; age: 66 ± 6 years, BMI: 33.8 ± 3.8 kg/m² (mean $\pm$ SD) completed this investigation. Compared with the prolonged sitting only condition, the implementation of seated arm ergometry every 30 minutes significantly reduced mean [95% CI] blood glucose iAUC (from 7.4 [5.2, 9.5] mmol·L⁻¹·h to 3.1 [1.3, 5.0] mmol·L⁻¹·h, $p = 0.001$). Significant reductions in mean insulin iAUC (from 696 [359, 1032] mU·L⁻¹·h to 554 [298, 811] mU·L⁻¹·h, $p = 0.047$) were also observed.

Conclusion: Performing short bouts of arm ergometry during prolonged sitting attenuated postprandial glycaemia despite maintaining a seated posture. This may have clinical significance for those with weight bearing difficulty who may struggle with postural change.

Trial registration: ClinicalTrials.gov (NCT02909894)

INTRODUCTION

Greater time spent sedentary (defined as sitting or reclining with low energy expenditure⁽¹⁾), is increasingly being recognised as an independent risk factor for morbidity (especially type 2 diabetes)⁽²⁻⁵⁾ and mortality^(2, 4-6), associations that persist after controlling for moderate-to-vigorous physical activity levels⁽²⁻⁵⁾. However associations between sedentary behaviour and health may be attenuated when engaging in very high levels of physical activity (typically in the region of ≥ 60 min/day)⁽⁶⁾.

Epidemiological findings have been strengthened by recent experimental evidence showing beneficial effects of interrupting prolonged sitting on markers of metabolic health, particularly postprandial glycaemia. For example, interrupting sitting time with regular bouts of light intensity⁽⁷⁻¹⁰⁾ and moderate intensity^{(8) (11-12)} walking have shown to be effective at reducing postprandial blood glucose levels in overweight and obese adults⁽⁸⁾, in those with dysglycaemia^(7, 12), diagnosed type 2 diabetes⁽¹⁰⁾, and in healthy, normal-weight populations^(9, 11). Breaking up prolonged sitting time with standing^{(7) (13-14)} or light resistance activities⁽¹⁰⁾ (while in a standing posture), have also proven to be effective.

Interrupting sitting time with upright (non-seated) activities therefore appears to be a viable way of attenuating postprandial glucose. Whether these improvements can be replicated by introducing upper body muscle activity while maintaining a seated posture is currently unknown. Addressing this question will help clarify whether it is the posture of sitting that is driving the association with poor health or whether it is the resulting generalised muscular inactivity. Importantly, investigating non-weight bearing strategies for reducing sedentary behaviour will also have important clinical implications for individuals who have restricted mobility or find standing difficult. In addition, strategies for breaking sedentary behaviour that have been investigated to date not only overlook those with weight bearing difficulty,

but have also been criticised for being disruptive and non-conducive to the working day⁽¹⁵⁾.

Given that seated strategies would not require vacating the desk area, this could pose as a more appealing option for sedentary workers.

The aim of this study is to investigate whether performing short, frequent bouts of seated upper body activity (using similar energy expenditures to light intensity walking) can attenuate postprandial glycaemia.

MATERIALS AND METHODS

Trial design

Each participant attended the research centre on three separate occasions between May and August 2016. The first visit involved consent, familiarisation and energy expenditure measurement. This was followed by two experimental condition visits that were at least 7 days apart. A randomised cross-over design was used whereby each participant took part in two experimental treatment conditions in a random order, thereby acting as their own controls. Order randomisation was conducted by a statistician using an online tool. Due to the nature of the trial, participants were not blinded to their randomised order, however all outcomes including blood assays were analysed blinded to the experimental condition that they derived from. Prior to commencing, this study received ethical approval from the National Health Service (NHS) East Midlands - Leicester South Research Ethics Committee. This trial was registered with ClinicalTrials.gov (NCT02909894).

Participants

Fourteen obese adults (BMI $\geq 30\text{kg/m}^2$) deemed to be inactive (failing to meet physical activity guidelines for MVPA, defined as 150 minutes per week of self-reported moderate intensity physical activity or 75 minutes per week of self-reported vigorous intensity physical activity⁽¹⁶⁾) and at high-risk of type 2 diabetes according to the Leicester Practice Risk Score

(LPRS)⁽¹⁷⁾ were identified and recruited from a database⁽¹⁸⁾. The LPRS calculates risk of type 2 diabetes based on six variables (age, sex, ethnicity, BMI, family history of the disease and antihypertensive drug usage), all individuals eligible for this study scored within the top 10% for risk within their family practice.

Exclusion criteria were as follows; an inability to communicate in spoken English, diagnosed type 2 diabetes, cardiovascular disease, psychotic illness, pregnancy, steroid usage, regular smoking habit or an inability to walk without an assistive device.

One individual was withdrawn due to having an HbA1c indicative of T2DM. This left thirteen participants who went on to complete the trial. This process is detailed in **Figure 1**.

Figure 1 – CONSORT diagram showing participant flow

Consent, familiarisation and energy expenditure (EE) assessment visit

On arrival, a researcher described in detail all study procedures and written informed consent was obtained.

As a part of the screening process, a venous blood sample was taken to assess glycated hemoglobin (HbA1c) levels, and confirm absence of type 2 diabetes ($<6.5\%$ [$<47.5\text{mmol/mol}$])⁽¹⁹⁾. Body weight (Tanita TBE 611: Tanita, West Drayton, U.K), waist circumference (midpoint between lower costal margin and iliac crest) and height were measured to the nearest 0.1kg, 0.5cm and 0.5cm, respectively.

During this first visit, we also undertook arm ergometry EE testing. Specifically, we sought to identify the power output (watts) necessary to elicit the desired EE during the main experimental condition. To allow comparison of metabolic responses to arm ergometry with previous findings that have examined the impact of light walking (3 km/h)⁽⁷⁻¹⁰⁾; we aimed to match participants' arm ergometry EE to their 3 km/h walking EE. To achieve this, EE was captured: a) while at rest b) while walking at 3km/h and c) while performing arm ergometry at various power outputs. In order for EE to be derived throughout each of these three domains, participants wore a face mask that was directly attached to a breath-by-breath gas-analysis system (Metalyser 3B, Cortex Biophysik, Leipzig, Germany). Herein, oxygen uptake and carbon dioxide production were used to calculate EE via indirect calorimetry⁽²⁰⁾. Before undertaking each testing occasions (detailed below), the gas analyser was calibrated according to the manufacturer's recommendations.

In order to assess EE while at rest (phase a), each participant sat quietly (refraining from movement) for 30 minutes. Expired gas data was collected over the final 15 minutes of this 30 minute period once values had stabilised.

In order to assess EE while walking at 3km/h (phase b), participants wore the face mask while walking on a motor driven treadmill (Technogym Excite® 700) for ten minutes. Expired gas data was collected in the latter 5 minutes.

In order to assess EE during seated arm ergometry (phase c), participants wore the face mask while pedalling at various wattages on an arm ergometer (Monark Rehab Trainer 881 E, HaB International Ltd, Warwickshire, UK). Participants performed three 5 minute bouts of arm ergometry, with the first bout standardised to a wattage of 15W for 5 min. For the remaining bouts, investigators manipulated the resistance of the arm ergometer and/or the speed at which the participants pedalled until the wattage of arm ergometry initiated an EE that matched that of light walking (this ranged from 15 - 35W). Expired gas data was collected in the 2nd 3rd and 4th minute, discarding both the first and last minute from each bout. The face-mask was removed for 5 minutes in between each bout in order for EE outputs to return to their resting level prior to the next measurement. From these three bouts, the wattage of arm ergometry that most closely resembled the average EE of light walking was prescribed in the subsequent experimental condition.

Finally, participants were issued a GENEActiv accelerometer (ActivInsights Ltd, Cambridgeshire, UK) to wear on their non-dominant wrist for 24 hours/day for 7 consecutive days, allowing quantification of habitual physical activity and sedentary behaviour levels.

Experimental procedure

Participants were asked to avoid alcohol and caffeine for 48 hours preceding experimental conditions and to replicate their diet in the 24 hours before main trials. Given that the influence of an acute bout of physical activity on insulin sensitivity can persist for 48 hours

⁽²¹⁾, avoidance of moderate and vigorous physical activity (MVPA) for this timeframe was also instructed. GENEActiv accelerometers were worn in the 2 days leading up to each experimental condition to confirm compliance with the exercise restriction. Participant's fasted from 10pm on the evening before main trials with only water permitted to drink.

The two experimental treatment conditions that formed this repeated measures crossover trial were as follows:

1) Prolonged sitting only - participants sat in a designated room for 7.5 hours (occupied with a desk, books, and laptop with internet services) while minimising excessive movements. Lavatory breaks were permitted using a wheelchair to and from the lavatory to further reduce unnecessary movements that could confound the study.

2) Arm ergometry breaks - participants emulated the 7.5 hour prolonged sitting condition, but every 30 minutes they performed 5 minutes of arm ergometry. These bouts were performed 12 times, totalling one hour of seated upper body activity and 6.5 hours of sedentary time throughout the course of the experimental day. As mentioned previously, the intensity of arm ergometry performed was dictated by phase b) and c) of the EE testing performed during visit one. The selected arm ergometry intensities closely resembled the EE achieved during that of the 3km/h light intensity walk for each participant.

On arrival at the research centre, participants had a cannula fitted into an accessible vein from which 10mL samples were obtained throughout the day. Immediately following the two fasting samples (depicted at time points -1 and 0 in **Figure 2**), participants were given a standardised breakfast meal consisting of 8kcal per kilogram of body weight, with a macronutrient composition reflective of co-ingestion in modern western diets (14% protein,

51% carbohydrate and 35% fat). Once breakfast had been consumed (within ≤ 15 minutes), blood sampling commenced at 30, 60, 120, and 180 minutes thereafter, enabling us to capture the postprandial period. An identical lunch meal was then issued (time point 3 in **Figure 2**) and sampling continued in the same fashion at 30, 60, 120 and 180 minutes afterward. Participants were supervised by study staff to ensure compliance with the protocol and were asked to wear an activPAL monitor to objectively confirm sitting time during both experimental conditions. *Ad libitum* water consumption was made consistent between conditions.

Measuring mood during experimental conditions

The Feeling Scale ⁽²²⁾ was used to quantify mood/affect prior to each blood sample (10 times in total) for both experimental conditions. Participants were asked to estimate their current mood state on an 11-point scale (very good= +5, 0 = neutral and very bad= -5) throughout the day.

Safety

Incidences of hypoglycaemia (defined as glucose levels below 4 mmol/L) during the final measurement period before lunch (3 hours post breakfast) and in the final measurement period of the day (3 hours post lunch) were also investigated during each experimental condition.

Free-living activity monitor processing

ActivPAL proprietary software (activPAL Professional V5.9.1.1) was used to create processed csv event files in order to quantify postural data collected during the 7.5 hour experimental conditions. GENEActiv .bin files were analysed with R-package GGIR version 1.2- 11

(<http://cran.r-project.org>) ^(23–24). Habitual data were included if participants had over 16

hours of wear-time recorded during the 24 hour day of interest, and if they had more than 3 valid days of data collected. Moderate to vigorous physical activity was calculated using an acceleration threshold of 100 mg⁽²⁵⁾. MVPA bouts were identified as ≥ 10 min of consecutive 5 second epochs where 80% of epochs were equal to, or higher than, the 100mg threshold. Time spent in 0- 50mg and 50 – 100mg was used to establish sedentary (minus sleep time) and light activity, respectively.

A summary of all GENEActiv data collected at each phase of the study is detailed in

Supplementary Table 1. ActivPAL data collected during experimental conditions is detailed in **Supplementary Table 2.**

Biochemical analysis

Glucose (primary outcome measure) was analysed on the day of collection by the University Hospitals of Leicester pathology department using standard quality controlled enzymatic assays with commercially available kits (Beckman, High Wycombe, U.K).

Centrifugated plasma samples (spun at 3,000g for 10 minutes immediately following extraction) were stored in -80°C freezers. Insulin (secondary outcome measure) was analysed from these collectively at the end of the trial using an electrochemiluminescence assay (Meso Scale Discovery). Each sample was ran in duplicate to ensure reliability of readings. Duplicate sample values with $\geq 20\%$ variability were reanalysed. Ambient conditions of the laboratory were kept consistent.

Sample size

The primary aim of this study was to assess the difference in postprandial glucose levels between the two experimental treatment conditions. Assuming a population standard deviation of 2.5 mmol·L⁻¹·h in glucose iAUC and a within-person correlation of 0.5, 13

participants were required to complete the study in order to detect a difference of $1.8\text{mmol}\cdot\text{L}^{-1}\cdot\text{h}$ in blood glucose iAUC between the experimental conditions with 90% power ($\alpha=0.05$).

Statistical analysis

Missing glucose and insulin data during the experimental conditions (highlighted in Supplementary Table 3) resulted from an inability to draw enough blood from the cannula at given time points and accounted for roughly 3.7% of required samples (19 out of 520). These 19 missing data points were imputed via a regression model used previously ⁽⁷⁾. The iAUC of glucose and insulin was calculated for each experimental condition. Total AUC was calculated by applying the trapezium rule. Subtraction of the fasting area from this total then gave a single value representing incremental AUC for each participant. Utilising iAUC as opposed to total AUC is common practice in acute interventions where fasting levels should be unaffected by the intervention ⁽²⁶⁾. Each outcome (glucose and insulin iAUC) was compared between treatments using a paired samples t-test. Data from the feeling scale were averaged across each condition and analysed using a paired t-test. All statistical analyses were performed using IBM SPSS Statistics (Version 22.0) and statistical significance was set to $p < 0.05$ throughout. Data distribution was interpreted by visual inspection and through the Shapiro-Wilk test. Normally distributed descriptive data and experimental data are presented as Mean $\pm$ SD and Mean (95% CI), respectively, while all non-parametric data is reported as Median (IQR) unless specified otherwise. For the experimental data, the unstandardized residuals were checked for normality.

RESULTS

Descriptive characteristics of those who completed this study are summarised in **Table 1** ($n = 13$). The study characteristics show that the energy expenditure of arm ergometry breaks conducted in the experimental condition was similar to that achieved through a light intensity walk at 3km/h (4.5 vs 4.6 kcal/min, respectively), however the average Respiratory Exchange Ratio (RER) was higher during arm ergometry compared to light intensity walking (1.00 vs 0.84, $p < 0.001$).

Experimental data

Biochemical results collected during each experimental condition are presented in **Figure 2**. The mean (95% CI) glucose iAUC response during the arm ergometry breaks condition (3.1 [1.3, 5.0] mmol·L⁻¹·h) was significantly lower than the mean glucose iAUC response to the prolonged sitting only condition (7.4 [5.2, 9.5] mmol·L⁻¹·h), $p = 0.001$. This was also the case for mean insulin iAUC (554 [298, 811] mU·L⁻¹·h vs 696 [359, 1032] mU·L⁻¹·h, $p = 0.047$).

Physical activity and sedentary time data

Physical activity and sedentary behaviour data is displayed in **Supplementary Table 1**. Free-living accelerometer data collected after the familiarisation visit ($n = 13$), showed that participants spent on average 644 ± 106 min/day sedentary and only engaged in 2 [0, 13] min/day of purposeful MVPA, thus confirming the inactive nature of this study cohort.

MVPA data collected in the two days leading up to the prolonged sitting only condition (0 [0, 10] min/day) and in the two days leading up to the arm ergometry breaks condition (0 [0, 7] min/day) confirm adherence to the standardised exercise restriction.

Mood, tolerance and safety

Mean $\pm$ SD self-reported feelings throughout the day were 3.1 ± 1.1 and 2.7 ± 1.2 for the prolonged sitting only and arm ergometry breaks conditions, respectively ($p = 0.101$ for difference), demonstrating positive mood states during both conditions. All participants completed the required number of arm ergometry bouts, and none reported musculoskeletal pain or discomfort.

Two participants did have asymptomatic hypoglycaemia during the final measurement of the day during the arm-ergometry breaks condition with no incidences reported during the prolonged sitting condition.

Table 1: Metabolic, demographic, and anthropometric characteristics taken at familiarisation alongside important in-study characteristics

Characteristics	Overall (n = 13)
Age (years)	66 ± 6
Female	7 [54]
BMI (kg/ m ²)	33.8 ± 3.8
Body weight (kg)	93.2 ± 13.2
Waist circumference (cm)	105 ± 16
HbA1c (%)	5.5 ± 0.4
HbA1c (mmol/mol)	37 ± 4
Total cholesterol (mmol/L)	4.6 ± 0.6
Resting heart rate (bpm)	60 ± 6
Systolic blood pressure (mm Hg)	140 ± 13
Diastolic blood pressure (mm Hg)	79 ± 9
White European	13[100]
Experimental characteristics	
Energy intake per experimental meal (kcal/meal)	746 ± 106
Prescribed power output of arm ergometry (Av.Watts)	20 ± 4
Energy expenditure while walking at 3km/h (Av.kcal/min)	4.6 ± 1.0
Energy expenditure at prescribed wattage of arm ergometry (Av.kcal/min)	4.5 ± 0.9
Av. Respiratory Exchange Ratio while walking at 3km/h (VCO ₂ /VO ₂)	0.84 ± 0.07
Av. Respiratory Exchange Ratio at prescribed power output of arm ergometry (VCO ₂ /VO ₂)	1.00 ± 0.07

Data are presented as Mean ± SD or n [%]

Figure 2 – Analyte AUC data between experimental conditions

DISCUSSION

This study is the first to investigate the metabolic impact of interrupting postprandial prolonged sitting time with regular bouts of upper body activity while remaining seated. Our results show that introducing 5 minutes of arm ergometry every 30 minutes while remaining in a seated posture is well tolerated and can attenuate postprandial blood glucose and insulin levels by approximately 57% and 20% respectively compared to that of prolonged sitting only. The fact that the observed reductions in glucose coincided with reductions in insulin concentration is suggestive of improved insulin sensitivity during the seated activity breaks condition using upper body muscle activation.

Our findings are consistent with the majority of experimental research to date. For example, experimental studies that have interrupted prolonged sitting with 3km/h walking breaks have led to clinically significant reductions in postprandial blood glucose by 28% ⁽⁷⁾ when implemented for 5 minutes every 30 minutes; by 39% when implemented for 3 minutes every 30 minutes ⁽¹⁰⁾ and by 16% ⁽⁹⁾ to 24% ⁽⁸⁾ when implemented for 2 minutes every 20 minutes post-meal. Our findings add to this evidence by demonstrating that regular bouts of seated arm ergometry may also be a viable method of improving postprandial glycaemia. Moreover, despite closely matching the energy demand of arm ergometry breaks to that of the 3km/hr walking bouts used in previous studies, we achieved a larger reduction in postprandial glucose iAUC than observed in these studies, even compared to those operating activity breaks at the same time intervals ⁽⁷⁾.

Given that arm ergometry breaks were implemented while maintaining a seated posture, our findings could not have been driven by postural change, and benefits to postprandial glycaemia may be attributed to other factors. For instance, physical activity breaks are

accompanied by increases in muscle activation. These increases in muscle activation not only raise energy expenditure but also increase blood flow and upregulate GLUT-4 expression in a dose dependant manner, which helps to restore homeostasis of postprandial glycaemia ⁽²⁷⁻²⁸⁾. Greater intensity of muscle activation in the smaller muscle mass during arm ergometry may have been necessary to achieve the same energy expenditure elicited by a 3km/hr walk. In turn, this greater muscle activation may have compensated for the limited muscle mass involved, and may explain the enhanced blood glucose utilisation observed here. This was supported in the present study by the higher RER observed during the arm ergometry compared to the energy matched walking, suggesting a greater relative intensity. Previous research has shown that enhanced postprandial blood glucose regulation is observed following higher intensity physical activity bouts compared to energy matched lower intensity physical activity bouts ⁽²⁹⁻³¹⁾. Thus, the higher intensity of arm ergometry, compared to light walking, may have helped augment reductions in postprandial glucose. Further research is therefore needed to assess whether reductions in postprandial glucose are also observed when using arm ergometry at a perceived light intensity.

The current study suggests an alternative strategy to help regulate postprandial glycaemia while sitting in a population at high risk of type 2 diabetes. Not only are arm ergometry breaks an alternative strategy, but they may even act as a sole strategy for individuals with weight bearing difficulty such as wheelchair users and those with severe peripheral neuropathy, which is thought to affect up to half of all people diagnosed with T2DM ⁽³²⁾. Given the disruptive nature of alternative strategies such as frequent walking breaks, seated activity may also appeal to office workers who find it difficult to leave their desk or office space at regular intervals throughout the day. Portable lightweight desktop arm ergometers

may also be of use in a hospital environment to improve postprandial glycaemia of patients who are bed bound yet able to sit upright.

The main strength of this study lays in the exploration of a novel strategy to alleviate the deleterious impacts of prolonged sitting bouts on postprandial glycaemia in a population at high risk of developing type 2 diabetes recruited through a primary care setting. However, it is important to acknowledge some limitations.

Although comparing our findings to those observed when introducing 3km/hr walking breaks ⁽⁷⁻¹⁰⁾, we did not include a third experimental walking condition which may have strengthened our conclusions. In addition, this study was not designed to elucidate potential mechanisms underpinning the acute reductions in postprandial glucose and insulin concentrations observed when employing seated activity breaks. However, this study was specifically designed to establish proof-of-concept for the efficacy of employing seated arm ergometry breaks as a method of acutely reducing postprandial glucose concentrations during prolonged sedentary behaviour. This is clinically important given that exaggerated postprandial glucose oscillations are associated with the development of type 2 diabetes ⁽³³⁾, cardiovascular disease ⁽³³⁻³⁵⁾ and obesity ⁽³³⁾. Even small elevations in postprandial glycaemia are thought to contribute to the development of atherosclerosis and subsequent coronary heart disease events ⁽³⁶⁾.

While a sample size of 13 provided adequate power for comparison between experimental conditions, the small sample makes it harder to generalise findings beyond the specific subject population recruited to this study. Given that efforts to manipulate blood glucose control are thought to be more pronounced in those with worse glycaemia ⁽³⁷⁾, the potential of such interventions in a diagnosed type 2 diabetes population would also be intriguing and

warrants further investigation. Future intervention studies observing the impacts of seated activity breaks using more ecologically valid regimes in settings outside of the laboratory (such as the home, or in a hospital environment) would also be of interest. The ability to emulate reductions in postprandial glycaemia through regular bouts of electro-stimulated muscular contractions would also be an interesting focal point for future research given recent links to improved insulin sensitivity⁽³⁸⁾ and its potential application to non-weight bearing populations. Likewise, given that arm ergometers are not easily accessible to all, engaging in seated upper body resistance band exercises could also pose as an intriguing alternative for future research. Future research exploring the minimal time, frequency and intensity that activity breaks can be implemented to bring about clinically significant improvements in postprandial glycaemia is warranted to promote more attractive, feasible and sustainable strategies. In addition, given that two subjects were found to be over the threshold for asymptomatic hypoglycaemia at the end of the arm ergometer condition, the safety of the current regime needs further investigation in those with a high risk or diagnosed T2DM, particularly in the 24 hours following the intervention. Further research utilising hyperinsulinaemic-euglycaemic clamp techniques could also be used to give more detailed insight into the dynamics of glucose metabolism when employing seated upper body breaks during prolonged sedentary behaviour.

In conclusion, this study demonstrates that seated arm ergometry breaks are a viable way to attenuate postprandial glycaemia. This suggests that breaking up the posture of sitting may not be necessary to elicit glycaemic benefit and that interventions to reduce sedentary behaviour should not focus solely on postural change.

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Author contributors

Conceived and designed the research question: MM TY CLE. Collected the data: MM.

Interpreted the data: All authors: Processed accelerometer data: CLE AR. Analysed the data: MM TY CLE. Drafted initial version: MM. Revised for important intellectual content: All authors.

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Conflict of interests

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Aside from the information disclosed above, authors declare no competing interests.

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