

ORIGINAL ARTICLE

Long-term change in respiratory function following spinal cord injury

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Study design: Retrospective study.

Objectives: To model the effect of time since injury on longitudinal respiratory function measures in spinal cord injured individuals and to investigate the effect of patient characteristics.

Setting: A total of 173 people who sustained a spinal cord injury between 1966 and April 2013 and who had previously participated in research or who underwent clinically indicated outpatient respiratory function tests at the Austin Hospital in Melbourne, Australia, were included in the study. At least two measurements over time were available for analysis in 59 patients.

Methods: Longitudinal data analysis was performed using generalised linear regression models to determine changes in respiratory function following spinal cord injury from immediately post injury to many years later. Secondly, we explored whether injury severity, age, gender and body mass index (BMI) at injury altered the time-dependent change in respiratory function.

Results: The generalised linear regression model showed no significant change ($P=0.276$) in respiratory function measured in (forced) vital capacity ((F)VC) after the spinal cord injury. However, significant ($P<0.05$) differences in respiratory function over time were found when categorising age and BMI.

Conclusion: This clinical cohort with long-term, repeated measurements of respiratory function showed no significant overall change in respiratory function over 23 years. However, a decline in respiratory function over time was observed in subgroups of individuals older than 30 years at the onset of injury and in those with a BMI $> 30 \text{ kg m}^{-2}$.

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INTRODUCTION

Lesion-dependent loss of respiratory muscle innervation caused by spinal cord injury (SCI) leads to the immediate impairment of respiratory muscle functioning and an associated reduction in lung volume.¹ Respiratory impairment after SCI causes respiratory complications² such as pneumonia, atelectasis, pleural effusions, sleep-disordered breathing or symptoms such as dyspnoea, in 50–67% of the patients.³ Garshick *et al.*⁴ showed that during the first year post injury the respiratory system was the cause of death in 28% of the cases and in 22% of the cases thereafter. Pneumonia has been shown to be the most common cause of death in patients with a SCI.⁵ These respiratory complications during the first 2 years post injury have substantially decreased over the last 30 years, whereas respiratory complication rates in chronic SCI have not altered.⁶

Multiple factors may influence the high rate of respiratory complications in this population. Some of these include poor *a priori* respiratory function,^{7,8} changes in breathing mechanics,⁹ and reduction of the elastic properties of the thorax with increasing time post injury.^{10,11} Lesion level also seems to be involved, as it has been shown that lung function decreases⁷ and respiratory tract infections increase⁸ with higher lesion level. However, patients with a SCI are able to train their remaining muscles, which can result in substantial variability in respiratory function measures across time in patients with the same lesion level.¹²

Sinderby *et al.*¹³ showed no significant change in vital capacity from early (1–3 years) to later (10 or more years) time post injury in patients with tetraplegia. Other studies even showed large improvements in lung function during the first 6 months post injury, which became smaller thereafter.^{14–17} Resolution of the impact of spinal shock, usually during the first 4–6 months post injury, and thus lung function, could explain these findings.¹⁸ Nonetheless, there are little data describing the effect of time since injury on respiratory function in SCI.¹⁹ Therefore, the first aim of the study was to describe the change in respiratory function following the early changes after a spinal injury in a clinical cohort.

In subjects with a SCI, similar to the able-bodied population, respiratory function is influenced by parameters such as gender, body mass index (BMI), age and severity of the injury.^{13,20–22} However, whether these parameters influence the changes in (F)VC following a SCI have not yet been investigated. The bulk of the literature is based on cross-sectional comparison. Currently, little is known about factors influencing the change in pulmonary function across time in SCI individuals. A better understanding of these factors may improve therapeutic interventions and approaches (for example, patient selection or identification) to prevent respiratory complications and potentially decrease respiratory morbidity and mortality. Therefore, the second aim of this paper was to investigate the effect of age at

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injury, gender, BMI and severity of injury on the change in (F)VC after a SCI.

SUBJECTS AND METHODS

Study design and patient population

Clinical and research databases at the Austin Hospital in Melbourne, Australia, were used to identify patients with SCI who had participated in previous research or had outpatient respiratory function tests (RFTs) completed. Only patients who had a SCI and one or more RFTs with a known time since injury were included in this study. This data audit was approved by the Austin Health Human Ethics Committee.

Lung function measurements

Lung function measurements were made in an accredited respiratory function laboratory at the Austin Hospital. Spirometers were calibrated daily and RFTs made in accordance with the relevant ATS²¹ and ERS/ATS²³ recommendations at the time of data collection. Briefly, patients were instructed to exhale fully from total lung capacity, through a mouthpiece while wearing a nose clip, until three reproducible and acceptable measurements were registered. The highest measured value was quoted for further analysis. Analyses were performed on the forced vital capacity (FVC) if available. If the FVC was not reported, then the VC was substituted. Change over time was modelled from patients with at least two technically acceptable measures over time.

Statistical analysis

Descriptive statistics (mean, s.d., median and range) for group characteristics of all the included patients and the subset of patients who were included in the analysis were calculated separately. Severity of injury was categorised according to the DeVivo *et al.*²⁴ recommendations. Comparisons between the total sample and the subset with at least two repeated FVC values within 23 years since injury were made to examine any differences using *t*-tests and χ^2 as appropriate.

The longitudinal data were initially visualised in Microsoft Excel (The Austin Hospital, Melbourne, VIC, Australia) to explore how the available data were spread over time since injury at the date of the RFT. Stata12 (The Austin Hospital) was used to create a generalised linear regression model to describe the change in (F)VC over time. In this model, the (F)VC is the outcome variable, the time since injury is the predictor and the patient is the random variable, to account for all patient characteristics and individual variables.

Subsequently, regression interaction analyses were performed in Stata12 to investigate the influence of age and BMI at the time of injury, gender and injury severity on the change in (F)VC over time. Age at injury was split into three groups for the ages 18–30 years, 31–60 years and older than 60 years, following the recommendations of DeVivo *et al.*²⁴ BMI at the time of injury was also split into three groups according to standard BMI classification;²⁵ BMI < 25, BMI 25–30 and BMI > 30. Severity of injury was categorised according to the DeVivo *et al.*²⁴ recommendations; however, in the subgroup of patients selected for analysis, there were no patients with an AIS E injury. For each of the categories, the individual slopes of the change over time were calculated and then compared to determine whether the variable has a significant influence on the change over time in (F)VC.

RESULTS

In this study, 180 patients with one or more RFT measurements were identified. The time since injury was known for 173 patients who sustained a SCI between 1966 and April 2013. The corresponding RFTs were conducted between 1996 and September 2014. Of the 311 RFTs conducted, FVC was not available for 19, and therefore VC was substituted. The characteristics of the 173 patients are described in Table 1.

For analysis of the longitudinal data, we included the 59 patients (34%) who underwent two or more RFTs. Figure 1 illustrates the selection process of patients in this study.

Table 1 Patients' characteristics of the whole sample (*n* = 173) and the subset for analysis (*n* = 59)

	Total group	Group with two or more RFTs with cut point of 23 years post injury	P-value
N	173 ^a	59	
<i>Gender</i>			0.31
Male	131 (76%)	42 (71%)	
Female	42 (24%)	17 (29%)	
Mean age at injury in years (s.d., median, range)	36 (16, 33, 1–84)	40 (16, 37, 18–71)	0.04
Mean BMI in kg m ⁻² (s.d., median, range)	26.3 (5.7, 25.4, 15.9–52.9)	28.2 (6.8, 26.8, 16.0–52.9)	<0.001
<i>Smoking history</i>			0.09
Never smoked	64 (37%)	20 (34%)	
Stopped smoking	70 (40%)	30 (51%)	
Currently smoking	39 (23%)	9 (15%)	
<i>Severity of injury</i>			0.27
C1–C4, AIS A, B, C	30 (17%)	10 (17%)	
C5–C8, AIS A, B, C	69 (40%)	30 (51%)	
T1–S5, AIS A, B, C	29 (16%)	9 (15%)	
AIS D	38 (22%)	9 (15%)	
AIS E	3 (2%)	0 (0%)	
Unknown	4 (3%)	1 (2%)	

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; BMI, body mass index; RFT, respiratory function test. Data are *n* (%) unless otherwise stated.

^aPatients with known time since injury at each RFT; the number used to calculate proportions for other characteristics.

The frequency of RFT measures was anticipated to decrease over time after injury, and the 'density' or 'frequency' of the measures of (F)VC would affect the validity of the regression modelling. There is no agreed statistical technique to determine the optimum frequency of data samples in time series analysis such as that proposed for these data. As such, Figure 2 was constructed to facilitate visual inspection of data density and to select a cutoff point for analysis of the effect of time after injury. As illustrated below, there is a clear reduction in the frequency of data collection after 23 years, and therefore this time was chosen as the censoring time post injury.

Change in pulmonary function in SCI

Characteristics of the sample of those with two or more RFTs performed up to 23 years post injury ($n=59$) are described in

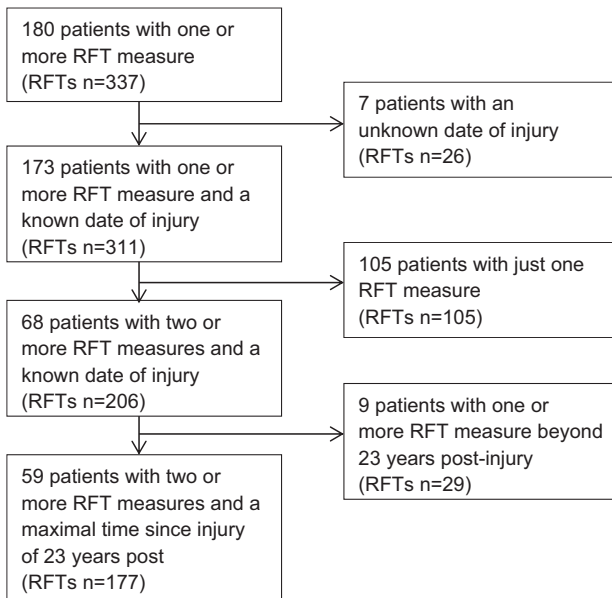


Figure 1 Selection of patients.

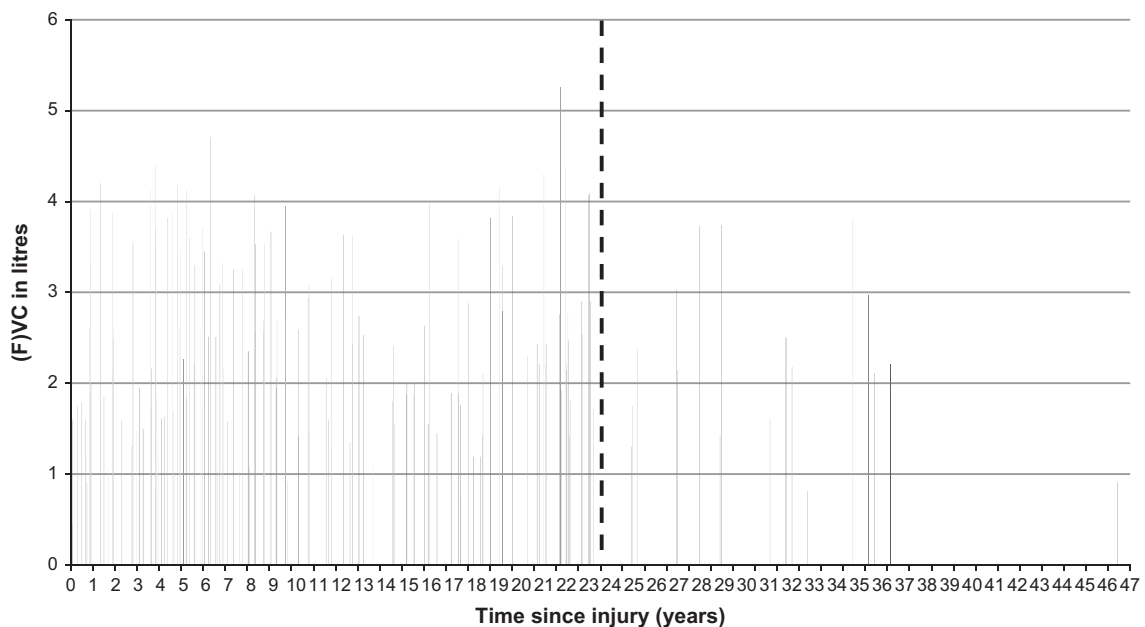


Figure 2 Individual (F)VC records plotted against time since injury.

Table 1 and compared with the total sample ($n=173$). Comparison of this subgroup with the total group shows that patients in the subgroup were on average 4 years older ($P=0.04$) and slightly more overweight ($P<0.001$).

Results from the linear model analysis showed a slope of -0.01 (s.e.m. 0.01, 95% CI: $[-0.03, 0.01]$; $P=0.28$), indicating that there was no significant change in (F)VC over time.

To assess the validity of substituting VC when FVC was unavailable, we performed a sensitivity analysis on the original data set, whereby we repeated the analysis using only those with two or more FVC measurement ($n=54$) and only those with two or more VC measurements ($n=42$). As with the primary analysis, these models showed no change in the respiratory function using either measure, with a FVC slope of 0.01 (s.e.m. 0.01, 95% CI: $[-0.03, 0.01]$; $P=0.48$) and a VC slope of 0.00 (s.e.m. 0.01, 95% CI: $[-0.02, 0.02]$; $P=0.99$).

Factors related to the change in pulmonary function in SCI

The characteristics of the different age, gender, BMI and injury severity categories of the subgroup of 59 patients are described in Table 2. Injury severity was unknown for one patient, who was therefore excluded from this analysis ($n=58$). The individual slopes for every category regarding change in (F)VC for every variable are plotted in Figure 3.

A significant difference was found when comparing the slopes between 18–30-year olds and 31–60-year olds ($P=0.003$). There were no differences between 18–30-year olds and those older than 60 ($P=0.222$) nor 31–60-year old and those older than 60 ($P=0.799$).

There was no difference in change in (F)VC over time between males and females ($P=0.16$).

When comparing BMI categories, a significant difference in change over time was found between people with a BMI $<25 \text{ kg m}^{-2}$ and $>30 \text{ kg m}^{-2}$ ($P<0.001$) and people with a BMI of $25\text{--}30 \text{ kg m}^{-2}$ and $>30 \text{ kg m}^{-2}$ ($P=0.024$). People with a BMI $>30 \text{ kg m}^{-2}$ showed a decline in (F)VC over time. No significant difference was found when comparing people with a BMI $<25 \text{ kg m}^{-2}$ and $25\text{--}30 \text{ kg m}^{-2}$ ($P=0.511$).

Table 2 Results from regression interaction analysis regarding age, gender, BMI and injury severity

Variable	Category	Patients (n)	RFTs (n)	Individual slopes	95% CI	P-value ^a
Age (years)	18–30	21	53	0.027	−0.004, 0.059	0.092
	31–60	29	88	−0.029	−0.049, −0.010	0.003
	>60	9	36	−0.020	−0.089, 0.049	0.570
Gender	Male	42	125	−0.014	−0.034, 0.006	0.156
	Female	17	52	0.001	−0.025, 0.027	0.934
BMI (kg m ^{−2})	<25	19	57	0.020	−0.005, 0.044	0.115
	25–30	21	57	0.005	−0.034, −0.043	0.821
	>30	19	63	−0.047	−0.071, −0.024	<0.001
Injury severity ^b	C1–C4, AIS A,B,C	10	28	−0.008	−0.043, 0.027	0.656
	C5–C8, AIS A,B,C	30	81	−0.002	−0.029, 0.024	0.857
	T1–S5, AIS A,B,C	9	34	0.001	−0.029, 0.031	0.929
	AIS D	9	30	−0.019	−0.071, 0.032	0.459

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; BMI, body mass index; RFT, respiratory function test.

^aThe listed P-value and CIs in the table test whether the gradient of the regression is statistically different to zero, that is, a straight (horizontal) line.

^bThe analysis regarding injury severity is based on 58 patients, since the 1 patient with unknown injury severity was excluded from this analysis.

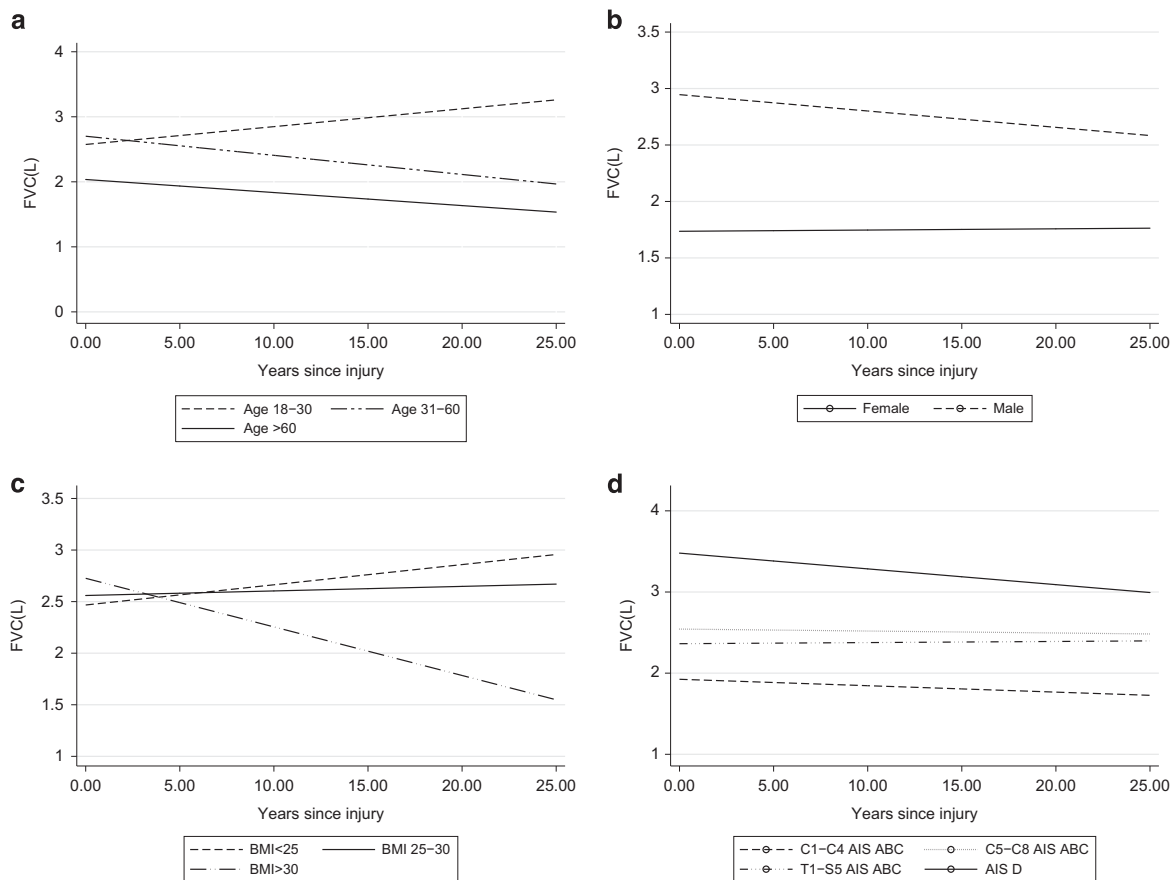


Figure 3 Interaction plots of (FVC over time (a) by age category, (b) by gender, (c) by BMI category and (d) by injury severity category.

When comparing the different categories of injury severity, no differences were found in change in (F)VC over time. Those with AIS D had a higher baseline pulmonary function than those AIS A,B,C with high cervical injuries.

DISCUSSION

This paper provides novel information regarding the change in respiratory function, specifically the (F)VC over time after SCI. We were able to model change over time in participants up to 23 years

after injury and have demonstrated that, after the initial drop in pulmonary function, little further changes are observed. However, specific groups of participants demonstrated particular patterns. Those participants with a BMI in the obese range at baseline and middle-aged subjects at the age of SCI onset showed a substantial decline in pulmonary function over time. This study provides novel and important insight into factors that alter the change in pulmonary function across time in a group of SCI individuals.

There have been few studies addressing issues regarding ageing and SCI in respiratory function.²⁶ Available data on this topic suggest that inspiratory capacity, and therefore FVC,²⁷ reduces after a SCI because of higher abdominal compliance. Consequently, this impacts functional residual capacity as the diaphragm is less elevated due to the lack of tone in the abdominal muscles. This is pronounced in individuals with tetraplegia and high-level paraplegia.²⁸ Mueller *et al.*²⁹ showed a decline in respiratory function with ageing in individuals with a SCI of -0.012 to -0.021 litres per year, which is less than that reported in able-bodied people (-0.026 to -0.043 litres per year).³⁰ Postma *et al.*³¹ showed that many patients with SCI have a larger decline in respiratory function in the first 5 years post injury, than can be explained by age-related decline. The results from both studies are in contrast with the finding of this study that respiratory function after SCI does not significantly decline. However, Mueller *et al.*²⁹ and Postma *et al.*³¹ only investigated a short follow-up of 1 year post discharge and 5 years post injury, respectively, which differs substantially from the current study follow-up time frame of up to 23 years post injury. Tow *et al.*,³² however, had a follow-up time of 20 years in their study, which did show a significant decline in vital capacity over the years. However, those authors only included tetraplegic patients, whereas in this study both tetra- and paraplegic patients were included.

In the second part of this study, we aimed to identify factors that may alter the change across time. Interestingly, we found significant changes over time between patients younger than 30 years of age and patients older than 30 years and between patients with a BMI of <30 and those with a BMI >30 . The fact that there was no statistically significant difference between age 18–30 and >60 was probably because of the small sample ($n=9$) of the oldest age group in this study and an associated poor statistical power. As such, it may be concluded that age >30 and a BMI >30 have a greater effect on the (F)VC decline over time.

The negative influence of a BMI >30 at baseline on the (F)VC over time is supported by the findings of Jones *et al.*,³³ who have shown that a BMI >30 negatively influences the vital capacity in able-bodied participants. Chen *et al.*³⁴ also showed that in an able-bodied population the respiratory function is decreased when overweight. This suggests that obesity importantly affects changes in respiratory function across time, an effect that is not altered by the presence of a SCI. Stolzmann *et al.*³⁵ have also demonstrated that longitudinal change in FVC is attributable to factors such as age and BMI. However, that study was only performed in male patients with SCI. In our study, both male and female patients with SCI were included; therefore, our results are applicable to all patients with SCI regardless of gender. Furthermore, no effect of gender was observed.

Clinical relevance

This study has shown the effect of time since injury on respiratory function in patients with SCI. As there is currently very limited published data available on the impact of time since injury, a better understanding of the physiology of respiratory function after SCI may provide insights for improved therapeutic interventions and respiratory care. These study results suggest that a serial decline in the respiratory function in a person with SCI may reflect a sign of disease, instead of normal ageing as typically observed in the able-bodied population. This study focused on the (F)VC because of its broad prognostic utility and relationship with possibly important outcomes like the need for intubation and tracheostomy.

Further, this study has shown that patients older than 30 at the time of their injury, and those with a BMI greater than 30, are likely to show a decline in respiratory function. In groups other than these, our data would suggest that any demonstrable decline in (F)VC may warrant clinical review.³⁶

Study limitations

It was not possible to determine which RFTs were performed for diagnostic or research purposes, and therefore it is impossible to exclude the possibility that some of the RFTs were completed when the patient was experiencing a respiratory complication (and therefore the RFT may reflect an underestimation of the true respiratory function). Further, no distinction was made in patients with or without pre-existing pulmonary diseases at the time of the RFT. These effects would be expected to have occurred at random across the entire data set and as such were unlikely to contribute to any systematic bias. Significant differences were found in age at injury and BMI when comparing the subset of 59 patients with the total group; however, these were small and unlikely to be clinically relevant.

Because of sample size limitations we were only able to assess the interaction between one independent variable with time since injury at a time, and therefore cannot control for confounding between variables. A larger study population would allow for controlling of more potentially explanatory variables in a multivariate mixed model analysis.

This study involved analysing a retrospective data set sourced from several databases at the Austin Hospital, and we were therefore unable to obtain reliable data on smoking history, ethnicity and change in BMI over time.

CONCLUSION

Investigation of longitudinal data of RFTs after SCI showed no overall change in (F)VC over time. Our clinical cohort data suggest that respiratory function in people with SCI does not change significantly beyond their initial drop in the lung function after injury. However, patients older than 30 years at the time of their injury and those with a BMI >30 are more likely to show a decline in respiratory function over time.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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