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Article Title: Incidence and Predictors of New Onset Constipation in Patients with Stroke versus Orthopedic Conditions during Acute Hospitalization: A Prospective Cohort Study

Short Title (Running Head): New Onset Constipation during Acute Hospitalization

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Incidence and Predictors of New Onset Constipation in Patients with Stroke versus Orthopedic Conditions during Acute Hospitalization: A Prospective Cohort Study

ABSTRACT

OBJECTIVES: Constipation is one of the most common medical complications of acute stroke. Currently, there is limited evidence to guide clinical management. The objectives of this study were to investigate the new-onset constipation in stroke versus orthopaedic patients and the predictors associated with constipation during acute hospitalization.

METHODS: A prospective cohort study of 110 patients comparing 2 cohorts: stroke patients (n=55) versus orthopedic patients (n=55). Both cohorts were matched by age and gender. Incidence of new-onset constipation occurred during patients' hospitalization was determined. Demographics, co-morbidities, mobility gain, fluid intake, laboratory parameters and use of medications were evaluated as possible predictors of constipation.

RESULTS: The incidence of new-onset constipation was high for both stroke and orthopedic patients respectively (33% versus 27%; p=0.66). Seven stroke patients (39%) and four (27%) orthopedic patients developed their first onset of constipation on Day Two of admission. In the multivariate analysis, mobility gain (RR 0.741, p<0.001), use of bedpan (RR 2.058, p<0.05) length of stay (RR 1.032, p<0.05) and use of prophylactic laxatives (RR 0.331, p<0.01) were predictors of the new-onset constipation.

CONCLUSIONS: New-onset constipation is a common complication of stroke and orthopedic conditions during acute hospitalization. Its early occurrence on Day Two of admission calls for an early preventive intervention. It is associated with length of stay, mobility gains, use of bedpan and prophylactic laxatives.

INTRODUCTION

Constipation is one of the most common medical complications of acute stroke (1, 2). It not only affects a person's physical well-being but also psychological well-being and quality of life, leading to a poorer outcome (3, 4). Despite its high prevalence, it is a neglected subject of research as it is often viewed as a non-life threatening condition. Constipation has been linked to many neurological diseases including stroke (5, 6). However, studies on constipation as a complication post-stroke and comparative study between stroke and other medical conditions are limited. The available studies were conducted either retrospectively, using cross sectional design or at post acute stage (1, 7, 8). As such, the incidence, causal relationships and relative risks among predictors of new-onset constipation during acute hospitalization remain uncertain. The management options for constipation in the stroke population are also limited due to few clinical trials (9). The objectives of this study were to investigate the incidence of new-onset constipation in patients with stroke versus orthopedic conditions and the predictors associated with constipation during acute hospitalization.

METHODS

STUDY DESIGN

A prospective cohort study was conducted comparing 55 consecutively screened patients in a stroke unit with 55 controls matched by age and gender from an orthopedic unit. In this study, we determine the incidence of constipation in these 2 cohorts during the period of hospitalization or during the first 4 weeks, whichever earlier. Possible predictors include: demographics, co-morbidities, length of stay, mini mental state examination

(MMSE), mobility gains, oral fluids, dysphagic, dysphasic, use of defecating devices and medications. Included patients from the stroke group were diagnosed with new onset of stroke by their primary neurologist and confirmed by Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI). The matched controls were recruited within a window period of 5 days to eliminate any changes that may occur within the two groups as a function of time. All included patients were ≥ 21 years old and recruited within 48 hours of their admission. Excluded from the study were patients with pre-existing gastrointestinal dysfunctions including constipation, fecal incontinence, pathological diseases or cancer of the colon or rectum. This study was approved by our local Centralized Institutional Review Board and funded by the Ministry of Health Nursing Research Committee with provision of written informed consent for all participants or their representatives.

OUTCOME MEASURES

Incidence of Constipation

Daily records of patients' symptoms were collected to determine the incidence of constipation within period of their hospitalization or the first four weeks, whichever earlier. Constipation was defined as: (1) having two or more of the following symptoms: straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, less than three defecations per week and requires manual maneuvers to facilitate defecations; (2) Loose stools were rarely present without the use of laxatives and (3) Insufficient criteria for irritable bowel syndrome.

Predictors of Constipation

- *Demographic data and co-morbidities* (diabetes, heart disease and previous stroke) were collected upon patients' admission.

- *Mini mental state examination (MMSE), dysphagic and dysphasic* status was assessed upon patients' admission.

- *Mobility gains* were obtained by subtracting the mobility score assessed using Functional Independence Measure (FIM) at the end of the study period from the score on patients' admission.

- *Laboratory parameters* (serum white blood cell and potassium) were recorded at first week of patients' admission.

- *Physical therapy (PT) sessions, oral fluid intake, use of medications* (antithrombotics, antacids, opioids, laxatives and NSAIDs) and *use of defecating devices* at each defecation were recorded during the study period.

SAMPLE SIZE CALCULATION

Based on an estimate of proportions from literature of prevalence study where the stroke group with constipation is at 30% and non-stroke group with constipation is at 8% (7), 50 patients per group were deem sufficient to achieve 80% power and a two-sided type I error of 5%. Further assuming a 20% drop out rate, this study aimed to recruit 120 patients (60 per group).

STATISTICAL ANALYSIS

Descriptive statistics for quantitative variables were presented as mean±sd, median and range and n (%) for categorical variables. Paired-Samples T Test will be used to compare

the quantitative variables between the 2 cohorts if normality assumption was satisfied otherwise Wilcoxon Signed Rank test was used. For categorical outcomes, McNemar Test was performed. The association between PT sessions and mobility gained was examined using Spearman Rank Correlation Coefficient. Univariate and multivariate conditional logistic regression analysis were performed to determine the association of constipation between possible predictors. Relative Risk (RR) with 95% CI will be presented. Data was analyzed using SPSS Version 18.0. Statistical significance was set as $p<0.05$.

RESULTS

A total of 120 patients (60 per group) met the inclusion criteria. Five matched cases were excluded from the analysis subsequently due to death (one stroke case); critical illness (two stroke cases and one control case) and new-onset of stroke (one control case). A total of 110 patients (55 per group) were studied (Figure 1).
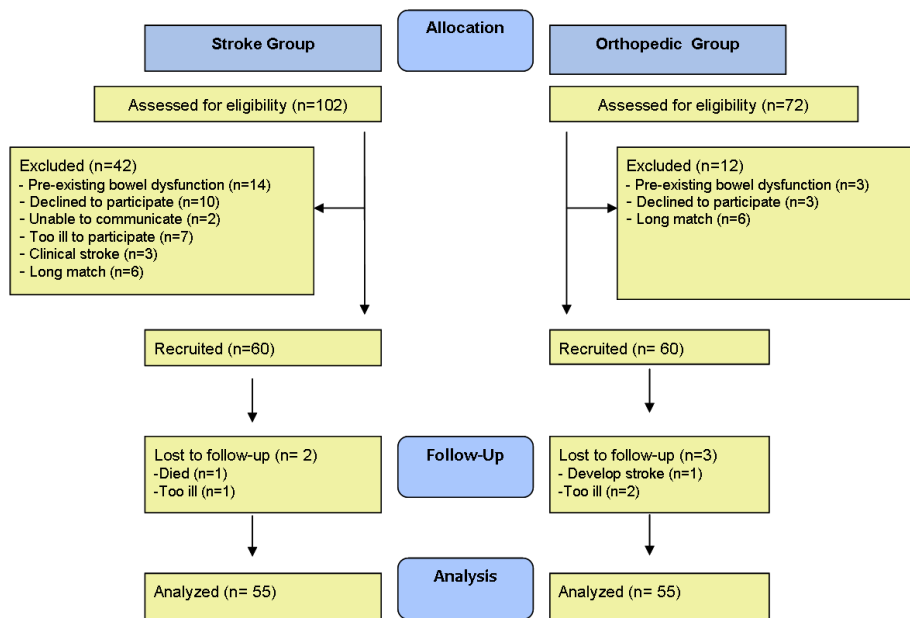
Figure 1. Flowchart of patient recruitment

Baseline Characteristics

Table 1 shows the baseline comparisons between the stroke group and controls. Their mean age were 61.2 $\pm$ 9.7 (stroke group) and 61.7 $\pm$ 9.6 (controls). The majority of the patient was males (60%). The stroke group had lower MMSE scores (p<0.001) and higher number of patients with previous stroke (p<0.05). There were no other baseline differences among the two groups.

Table 1. Patient Demographic and Baseline Data

Demographics	Stroke no (%) n=55	Orthopedic no (%) n=55
Age (mean± SD)	61.2 ± 9.7	61.7± 9.6
Gender		
Male	33 (60)	33 (60)
Race		
Chinese	43 (78)	44 (80)
Malay	6 (11)	6 (11)
Indian	6 (11)	3 (5)
Others	0	2 (4)
Marital Status		
Single	6 (11)	2 (4)
Married	42 (76)	49 (89)
Divorced	2 (4)	1 (2)
Widowed	5 (9)	3 (6)
Educational Level		
Degree	2 (3.6)	2 (3.6)
Diploma	3 (5.5)	7 (12.7)
Secondary	24 (43.6)	20 (36.4)
Primary	16 (29.1)	16 (29.1)
None	10 (18.2)	10 (18.2)
MMSE (mean± SD)	24 ± 5.1**	27±3.1
Co-morbidities		
Previous stroke	10 (18.2)*	0
Diabetes	20 (36.4)	16 (29.1)
Heart Disease	8 (14.5)	8 (14.5)

*P<0.05
**P<0.001

Incidence of New-Onset Constipation

The median length of stay for the stroke group was 8 days (range 2-70) and 4 days (range 2-15) for the controls (p=0.001). During hospitalization, 18 (33%) patients from the stroke group and 15 (27%) controls developed new-onset constipation (p=0.66). Seven patients (39%) from the stroke group and four (27%) controls developed the first onset of constipation on Day two of their admissions. Both groups developed constipation between Day 2 to Day 14 of their admissions. After Day 14, no patients developed constipation (Figure 2).

Figure 2. Day of Constipation in Patients with Stroke and Orthopedic Conditions During Acute Hospitalization
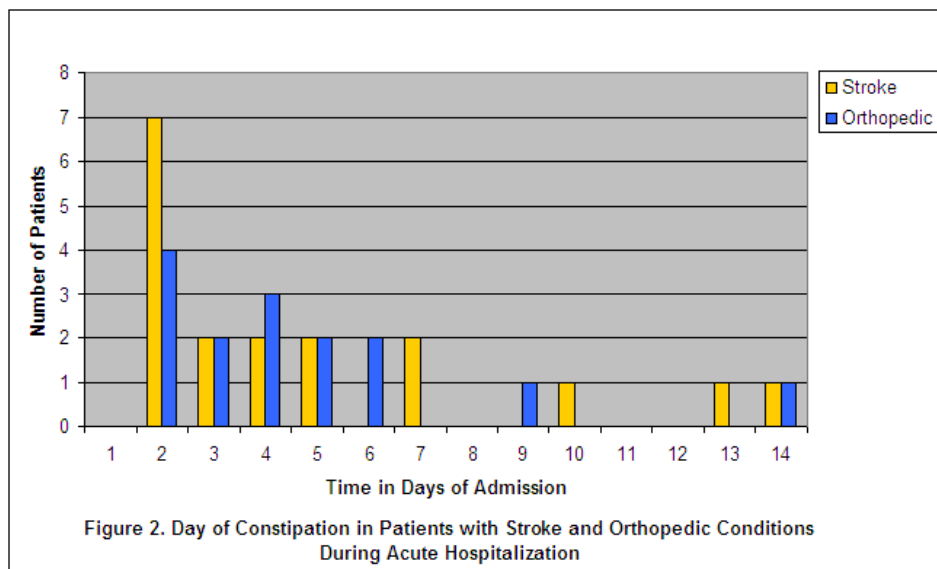
Predictors of New-Onset Constipation

Table 2 shows the demographic and clinical factors in patients with and without constipation. The risk of developing new-onset constipation was significantly higher in the Indian ethnic group as compared with Chinese. Patients, who were dysphagic, stayed longer in the hospital, used bedpan for defecation and used antacids have a higher risk of developing constipation whereas patients who used prophylactic laxatives, gained better mobility scores and consumed more oral fluid were less likely to develop constipation.

Ninety patients (81.8%) attended at least one PT session during the study period and the number of PT sessions was positively correlated with mobility gains (r_s=0.447; p<0.001). Twelve patients (10.9%) used bedpan for a certain time and 8 out of the 12 patients (66.7%) verbalized difficulty in defecating when using the bedpan. Forty-one patients (37.3%) were prescribed one or a combination of two or more prophylactic laxatives. The most frequently prescribed laxatives were lactulose (n=37) and sennosides (n=26) (Figure 3). Stroke, MMSE, dysphasic, use of antithrombotics, Opioids and NSAIDs, were not associated with the risk of constipation.

Table 2: Univariate Analysis on the Association Between New-Onset Constipation and Demographics, Clinical factors and Medications

Variables	Constipation No. (%) / mean ± SD / median (range)	No Constipation No. (%) / mean ± SD / median (range)	RR	95% CI	
Chinese	24 (27)	63 (72)	1		
Malay	3 (25)	9 (75)	0.927	0.361	2.377
Indian	5 (56)	4 (44)	2.150*	1.150	4.006
Others	1 (50)	1 (50)	1.677	0.259	10.855
Non-Stroke	15 (27)	40 (73)	1		
Stroke	18 (33)	37 (67)	1.200	0.695	2.073
MMSE	25 (12-30)	27 (9-30)	0.959	0.906	1.015
Dysphagic	13 (46)	15 (54)	1.881*	1.129	3.1.32
Dysphasic	1 (33)	2 (67)	1.103	.262	4.650
Length of Hospital Stay (LOS)	10 (3-70)	4 (2-48)	1.025**	1.012	1.038
Prophylactic Laxatives	7 (17)	34 (83)	0.452*	0.224	0.911
Mobility Gains	0 (0-5)	4 (0-6)	0.722**	0.620	0.839
Oral Fluid Intake	530±348	663±262	0.999*	0.998	1.000
Use of Bedpan	9 (75)	3 (25)	3.125**	2.061	4.739
Antithrombotics	19 (26)	54 (74)	0.701	0.403	1.220
Opioids	10 (23)	34 (77)	0.637	0.344	1.177
NSAIDS	10 (22)	35 (78)	0.630	0.331	1.201
Antacids	2 (67)	1 (33)	2.222*	1.018	4.850

*P<0.05   Non-significant variables: age, gender, co-morbidities and lab parameters
**P<0.001

Figure 3. Types of Prophylactic Laxatives Used During Acute Hospitalization
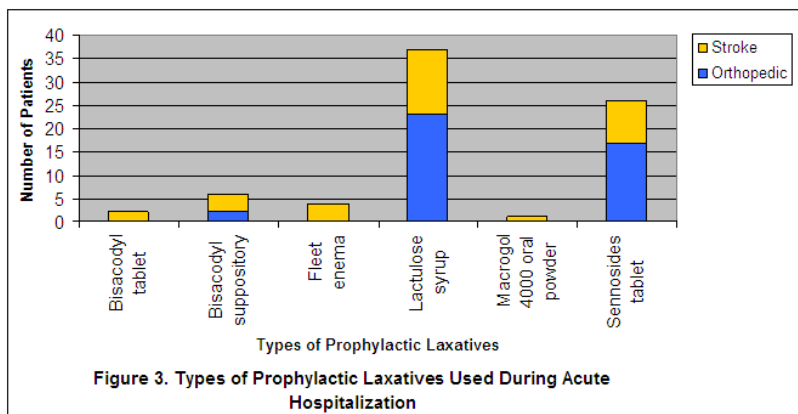
In the multivariate analysis, the following variables were included in the model: age, gender, race, stroke, co-morbidities, length of hospital stay, MMSE. mobility gains, oral fluid intake, dysphagic, dysphasic, use of bedpan, laboratory parameters, use of prophylactic laxatives, antithrombotics, opioids, NSAIDs and antacids. Length of stay, prophylactic laxatives, mobility gains and use of bedpan remained as significant predictors. For every one day increase in hospital stay, the risk of new-onset constipation would increase by 3.2% (95% CI: 0.6 % to 6.0 %). Patients who took prophylactic laxatives have their risk lessen by more than half compared to those without prophylaxis (95% CI: 15.5 % to 70.3 %). For every one point gained in FIM score, the risk also decreased by 25.9% (95% CI: 12.7 % to 47.0%). Patients who used bedpan for defecation were twice more likely to develop constipation compared with those who did not use bedpan (95% CI: 1.172 to 3.614) (Table 3).

Table 3: Multivariate Analysis on the Association Between New-Onset Constipation and Significant Predictors

Variables	P Value	RR	95% CI	
LOS	0.016	1.032	1.006	1.060
Prophylactic Laxatives	0.004	0.331	0.155	0.703
Mobility Gains	0.000	0.741	0. 630	0.873
Use of Bedpan	0.012	2.058	1.172	3.614

DISCUSSION

The incidence of new-onset constipation during hospitalization is considerably high for both groups, but lower as compared with previous studies of 55% to 60% (4, 10). These differences could be due to the variation in definitions and study periods. In clinical practice, healthcare practitioners often define constipation as bowel frequency less than three per week (7, 10) or absence of bowel movements for two or more consecutive days (1). However, symptoms such as straining and hard stools were strongly associated with

self-reported constipation (11) highlighting that stool frequency should not be the only criteria used to define constipation. Su et al, 2009 (4) defined constipation according to Rome II criteria and measured outcomes at four weeks. We defined constipation based on the symptoms from Rome III criteria and measured outcomes during patients' hospitalization or within the first 4 weeks, whichever earlier. As such, we were unable to adopt the duration criteria of Rome III where symptoms have to be present for the last 3 months with onset of at least 6 months prior to diagnosis. It is also challenging to manage patients with new-onset constipation clinically if treatment initiation is based on fulfilling the percentage criteria of Rome III e.g straining during at least 25% of defecations etc. Treatments are often sought by patients and initiated by physicians at first few instances of reported symptoms and not wait till patients fulfilled the percentage criteria. These suggest that Rome III criteria may have its limits for use on patients presenting with acute symptoms of constipation and with short hospital stay. Perhaps some modifications may need to be considered for it to be feasibly used to manage patients in acute clinical settings.

Stroke itself was not a predictor of new-onset constipation when compared with orthopaedic group in our study although some studies have indicated otherwise (7, 8). Instead, clinical and practical factors such as length of stay, prophylactic laxatives, mobility gains and use of bedpan were predictors of the new-onset constipation. Previous studies were using cross-sectional designs and measured prevalence of constipation. One study compared stroke with orthopedic patients with at least three months of physical immobility (7) whereas another study compared stroke with normal volunteers and

inpatients with non-neuro/gastro conditions a few hours of their admission (8). Our study compared stroke with orthopedic patients without pre-existing bowel dysfunction and prospectively followed them through their hospitalization measuring incidence of new-onset constipation.

Constipation is often associated with physical inactivity and low functional status (10). Physical exercises can enhance colonic propulsion (12) and regular exercise regimes improve defecation symptoms (13, 14). In this study, most patients attended at least one PT session and the number of PT sessions positively correlates with their mobility gains. The intensity and duration of the PT sessions vary according to patients' conditions. Mobility gains are the ultimate goal of the PT sessions and our findings indicate that higher mobility gains significantly reduce the likelihood of developing constipation. In clinical practice, it is difficult to pre-determine the degree of mobility or functional gains in each patient as it also depend on other factors such as severity of disability, cognitive status, psychological factors and length of stay etc (15-17). However, as early ambulation through standardized mobility protocol have shown to improve functional status from admission to discharge of hospitalized older adults and patients recovering from surgery (18), efforts could be directed to initiate early ambulation through PT. As to the amount of PT needed to achieve significant mobility gains however, need further investigation.

The use of bedpan is a common practice in hospitals. In acute care, it was found that 18.2% of patients used bedpan for a certain time during hospitalization. Departments that were frequently associated with the use of bedpans were orthopaedic and surgical wards

followed by medical wards (19). Patients who used bedpan were often confronted with pain and inconveniences (coldness and hardness of bedpan; uncomfortable positions and hygiene inconveniences) (20). In this study, the number of patients who used bedpan is relatively small (10.9%). Most verbalized difficulty in defecation using the bedpan especially in lying position. Body positioning can have a significant influence in successful defecation. In lying position, there is a dyssynergic pattern of defecation (paradoxical increase in anal sphincter and a rise in the intrarectal pressure) observed in healthy person which influence the expulsion of stool. In sitting position with distended rectum, a normal defecation pattern (a rise in intrarectal pressure that synchronized with relaxation of anal sphincter) is observed with the ability to expel stool (21). Moreover, a correct sitting position with legs adequately flexed in a commode or at a toilet opens the anorectal angle at its maximal width and further promotes defecation (22). The gravitational effect of sitting position also maximizes the use of voluntary control of intra-abdominal pressure which trigger increased activity in the enteric nervous system and influences the process of defecation (23). At times, the use of bedpan other than of a habit and convenience is also based on the assumption that patients may exert themselves more if they are to use alternatives such as a bedside commode. On the contrary, energy expenditure in terms of oxygen consumption was observed to be consistently higher while on a bedpan than a commode (24). Sitting position appears more effective than the lying position and thus practice protocol should perhaps extensively advocate the use of defecating devices that allows proper sitting positioning to promote normal defecation pattern. Future studies could also further explore the influence of positioning and

measure the individual contributions of abdominal muscles and pelvic floor muscles in promoting successful defecations.

Laxatives are often used to relieve existing symptoms of constipation and rarely as a prophylactic treatment except in some settings such as palliative care (25). In acutely hospitalized elderly patients, it was found that almost one third of them needed a laxative at least once every three days (26). Laxatives aid defecation by increasing stool volume (bulk), decreasing stool consistency (softening) and/or stimulate colon motility. In this study, we observed that prescribing prophylactic laxatives was not a standard practice in both stroke and orthopedic units although impaired mobility and use of pain medications are factors that could potentially increase the risk of developing constipation (27, 28). Our findings indicate that patients who were prescribed prophylactic laxatives were less likely to develop constipation. The two most commonly used laxatives were osmotics (lactulose) and stimulants (sennosides). These laxatives were used as a single agent or with a combination of two or more agents. There was no specific sequence of order on the types of laxatives prescribed. Some guidelines on managing chronic constipation recommended treatment starting with osmotic laxatives, stool softener and bulk-forming agents followed by stimulant laxatives as the last option when non-pharmacological treatment fails (29, 30). Laxatives are generally well-tolerated when used for treatment of chronic constipation (31). When used as a prophylaxis, it effectively reduces the incidence of opioid-induced constipation in cancer patients (32, 33) and critically-ill patients (34). Hence, perhaps one of the preventive measures is to consider using laxatives as a short-term prophylactic on acutely hospitalized patients with stroke and

orthopaedic conditions. Future studies should further explore the use of various short-term prophylactic laxatives and monitor its efficacy, tolerability and cost-benefits.

This study excluded patients who were critically ill and compared stroke with orthopaedic patients only. Subsequent studies could investigate subjects of other medical conditions where findings could be further generalized.

CONCLUSION

New-onset constipation is a common complication of stroke and orthopaedic conditions. Its occurrence is early and associated with length of stay, mobility gains, use of bedpan and prophylactic laxatives. This study serves as a reference for future larger scale studies in defining a hospital wide constipation protocol.

Study Highlights

1. WHAT IS CURRENT KNOWLEDGE

- Constipation is one of the most common medical complications after stroke

- Limited number of studies on constipation as a post stroke complication

- Incidence of new-onset constipation and predictors associated with constipation after stroke during acute hospitalization remain unclear

2. WHAT IS NEW HERE

- Incidence of new-onset constipation is high for both patients with stroke and orthopedic conditions during acute hospitalization

- The occurrence of new-onset constipation is as early as Day Two of admission

- Stroke is not a predictor of new-onset constipation when compared with orthopedic conditions

- Length of stay, mobility gains, use of prophylactic laxatives and use of bedpan are predictors of new-onset constipation

CONFLICT OF INTEREST

Guarantor of the article: Su-Fee Lim

Specific author contributions: Lim, Ng, Chan and Childs were involved in the study concept and design. Lim, Ong and Tan were involved in the planning and conduct of this study. Lim and Chan were involved in the analysis and interpretation of data. Lim, xxxx, were involved in writing the manuscript. All authors reviewed and approved the final manuscript.

Financial support: This research study is supported by Ministry of Health Nursing Research Committee. This work is independent of the funding agency.

Potential competing interests: None

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