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A prospective follow-up study of the association of radiation exposure with fatal and non-fatal stroke among atomic bomb survivors in Hiroshima and Nagasaki (1980–2003)

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ABSTRACT

Objective: Use of medical radiotherapy has increased markedly in recent decades. Whether the consequence includes an increased risk of cardiovascular disease remains to be determined. The purpose of this study was to examine the association between radiation exposure and the incidence of stroke among Japanese atomic bomb survivors.

Design: A prospective follow-up study.

Setting and participants: Radiation exposure from the atomic bombing was assessed in 9515 subjects (34.8% men) with 24-year follow-up from 1980. Subjects were free of prevalent stroke when follow-up began.

Outcome measures: Stroke events and the underlying cause of death were reviewed to confirm the first-ever stroke. Subtypes (ischaemic and haemorrhagic events) were categorised based on established criteria according to the definitions of typical/atypical stroke symptoms.

Results: Overall mean radiation dose (±SD) in units of gray (Gy) was 0.38±0.58 (range: 0–3.5). During the study period, 235 haemorrhagic and 607 ischaemic events were identified. For men, after adjusting for age and concomitant risk factors, the risk of haemorrhagic stroke rose consistently from 11.6 to 29.1 per 10 000 person-years as doses increased from <0.05 to ≥2 Gy (p=0.009). Incidence also rose within the dose range <1 Gy (p=0.004) with no dose threshold. In women, the risk of haemorrhagic stroke rose with increasing radiation exposure but not until doses reached a threshold of 1.3 Gy (95% CI 0.5 to 2.3). Among women, for doses <1.3 Gy, differences in stroke risk were modest (13.5 per 10 000 person-years), while it increased to 20.3 per 10 000 person-years for doses that ranged from 1.3 to <2.2 Gy and to 48.6 per 10 000 person-years for doses that were higher (p=0.002). In both sexes, dose was unrelated to ischaemic stroke.

Conclusion: While the risk of haemorrhagic stroke increases with rising radiation exposure for both sexes, effects in women are less apparent until doses exceed a threshold at 1.3 Gy.

ARTICLE SUMMARY

Article focus

- Use of medical radiotherapy has increased in recent decades.
- Whether the consequence includes an increased risk of cardiovascular disease is unknown.
- Our purpose was to examine the association between radiation exposure and the incidence of stroke among atomic bomb survivors in Japan.

Key messages

- Risk of haemorrhagic stroke increased with rising radiation exposure for both sexes, although effects in women were less apparent until doses exceeded a threshold at 1.3 Gy.
- Radiation exposure was unrelated to ischaemic stroke.

Strengths and limitations of this study

- This report provides information on the incidence of stroke using data from clinical examinations and mortality records following a structured research protocol.
- Measurement of radiation exposure adheres to a precise system of quantification.
- While best attempts were made to properly classify strokes outcomes, diagnostic uncertainties persist.

INTRODUCTION

Worldwide use of radiographic procedures in medicine has increased markedly in recent decades.[1–3] While health benefits are thought to outweigh the risk of adverse side effects, increased use of radiotherapy, particularly in the age range <65 years,[2] raises concerns over the promotion of a variety of adverse health outcomes, most notably cancer. Although equivocal, data from patient samples and occupational studies suggest that a corresponding rise could also occur in the incidence of circulatory disease and asymptomatic atherosclerosis.[4–11] Based on mail surveys and vital statistics records from the Japanese atomic bomb survivors Life Span Study (LSS), evidence indicates that radiation >0.5 gray (Gy) increases the risk of all-stroke death (1950–2003).[12] Associations that include gender effects and stroke subtypes, however, have not been clearly identified. Our purpose was to examine the association between radiation and stroke incidence among atomic bomb survivors in the Adult Health Study (AHS) from the Radiation Effects Research Foundation (RERF) over two decades (1980–2003). Stroke outcomes include morbidity and mortality from haemorrhagic and ischaemic events after adjustment for several concomitant risk factors.

METHODS

Study population

In 1950, the Atomic Bomb Casualty Commission (now the RERF) established the LSS of 120 321 survivors of the atomic bombings of Hiroshima and Nagasaki, Japan.[13] Follow-up is limited to periodic mail surveys and mortality outcomes from vital statistics data. In 1958, a series of comprehensive physical examinations was performed with the establishment of the AHS cohort consisting of 19 961 subjects from the LSS subjects. In the AHS, examinations have been given biennially with informed consent and approval from the RERF Ethics Committee. The AHS biennial health examinations provide clinical information complementary to death and tumour registries data. The AHS includes individuals exposed to a broad range of doses to enhance detection of radiation effects on a variety of disease outcomes. Participation rate has ranged from 70% to 90% throughout the examination cycles. For the current report, follow-up began at examinations that were given in 1980. From that time, subjects were followed for incident stroke over a 24-year period (until the end of 2003). Of the eligible 11 231 participants, 208 prevalent stroke (35 were haemorrhagic, 117 were ischaemic and 56 were of unknown origin), and 1508 without dose information were excluded. The final sample includes 9515 AHS participants.

Radiation dosimetry

Estimation of radiation dose exposure for each individual was based on an updated dosimetry system (DS02) that takes into account biases arising from errors in calculated doses, physical locations and organ shielding at the time of bombing.[14] For all analyses, weighted colon doses were used in units of gray (Gy), where the dose for an individual corresponds to the total exposure in γ rays + 10× the smaller neutron dose.[14] Colon dose was selected a priori because of broad (systemic) cardiovascular processes that are often associated with stroke. This includes the major system-wide precursors of hypertension, cigarette smoking, total cholesterol, diabetes and body mass. Colon dose was also used in an earlier study of circulatory disease in the RERF.[12]

Stroke ascertainment

Possible stroke events and the underlying cause of death were coded according to International Classification of Disease (ICD) in the RERF database. The ICD codes of stroke-related disease are 330–332, 334, 352 and 435 (ICD-7); 333, 430–434, 436 and 438 (ICD-8); 430, 431 and 433–438 (ICD-9) and G45, I60, I61, I63–66 and I69 (exclude I698) (ICD-10). Virtually all deaths are assumed accounted for based on access to a comprehensive nationwide registration of deaths in Japan. The number of missed cases of non-fatal strokes in subjects who remained alive at the close of follow-up (2003) is unknown, although with high participation across repeated AHS examinations, it is thought to be small. There is no indication of bias in the indexing of stroke by radiation exposure. All data (health examinations, death certificates and autopsy reports when available) were reviewed to confirm the first-ever stroke. Stroke was defined as an acute-onset focal neurological deficit of vascular aetiology, persisting for at least 24 h. Stroke subtypes (ischaemic and haemorrhagic events) were categorised based on established criteria that included clinical features, neuroimaging and non-invasive vascular studies, and other laboratory criteria according to the definitions of typical/atypical stroke symptoms in the WHO Monitoring of Trends and Determinants in Cardiovascular Disease Projects.[15] Ischaemic stroke was diagnosed if there was a focal neurological deficit in the absence of haemorrhage based on neuroimaging when the neuroimage showed an ischaemic infarct that correlated with the clinical deficit or an ischaemic infarct was documented at autopsy. Not all diagnoses of stroke were based on neuroimaging studies. Among all strokes, 49.0% were based on death certificates alone (50.2% for haemorrhagic stroke and 49.3% for ischaemic stroke).

Baseline examination and questionnaires

Baseline concomitant data included the age when follow-up began, systolic blood pressure (SBP), total cholesterol (T-CHO), body mass index (BMI), diabetes, smoking and alcohol intake. A priori selection of these risk factors was based on a perceived need to consider traditional stroke risk factors, to include adjustments[16–18] that were made in an earlier report from the RERF[12] and to consider possible sources of confounding due to documented relationships between radiation exposure, SBP[19] and T-CHO.[20] Except for smoking and alcohol intake, the concomitant data were collected at clinical examinations that were given in 1980. In the event that an examination cycle failed to coincide with 1980, information from the most recent examination was used (with 5 years). Measurement of non-fasting T-CHO is described elsewhere.[20] Sitting SBP was measured in the left arm. BMI was defined as weight (kg) divided by height squared (m). A diagnosis of diabetes was based on a physician diagnosis or the use of medications for diabetes.

Data on smoking and alcohol intake were collected from mail surveys that were administered from 1978 to 1980. In the absence of such data, information was taken from direct interviews in 1965. Smoking status was defined as never-, past and current smoker. Alcohol intake was defined according to typical Japanese consumption strata in units of ethanol as non-drinker, light drinker (<34 g/day) and heavy drinker (≥34 g/day).[21] For the sample with interview data from 1965 and the mail survey in 1978−1980, smoking status was unchanged in >87% of the study participants. In contrast, patterns of alcohol intake are more variable. The correlation between the repeated alcohol measures is 0.24, although it is highly significant ($p<0.001$).

Statistical methods

Crude and age-adjusted incidence of haemorrhagic and ischaemic stroke in person-years of follow-up were estimated across common ranges of radiation dose based on standard analysis of covariance methods.[22] Further description of the procedure used in the calculation of person-years is given elsewhere, along with its close relationship with a Cox proportional hazards regression model.[23] Similar methods are also useful for providing age-adjusted percents and average levels of the confounding risk factors across the radiation strata.[19]

The primary method for testing for an independent effect of radiation on the risk of each stroke subtype is based on Cox proportional hazards regression models where radiation dose is modelled as a continuous predictor variable. Although the number of strokes is often small (particularly haemorrhagic events), we found no evidence for a significant departure from the assumption of proportionality. This assumption is further relaxed by adjusting for age based on the use of attained age as the time scale in the non-parametric part of the hazard model, while radiation dose and the concomitant risk factors were modelled as covariates in the parametric part.[24] Concomitant risk factors included SBP and the other risk factors. Non-linear relationships between radiation dose and the stroke risk were also considered, including a threshold analysis. For the latter, dose was modelled as $(D-\delta) \times I_\delta(D)$, where D is a radiation dose, δ is a threshold and $I_\delta(D) = 1$ when $D\geq\delta$ and 0 otherwise. The dose that minimises $-2 \times$ the log likelihood provides a point estimate for δ. A 95% CI for δ consists of upper and lower threshold values for which $-2 \times$ the log likelihood differs from the minimum value by 3.84 (the 95th percentile from a χ^2 distribution with 1 degree of freedom). If the lower threshold value is >0 Gy, then a dose threshold is assumed to exist with 95% confidence. Although primary tests of significance were based on radiation dose being modelled as a continuous risk factor, patterns of association are also described through the use of indicator variables that allow for the estimation of the relative hazard of stroke (and 95% CIs) between radiation dose strata ≥0.05 Gy versus doses considered to be small (<0.05 Gy). All reported p values were based on two-sided tests of significance. Statistical modelling and testing were based on the use of SAS software (V.9.2; SAS Institute Inc.).

RESULTS

Radiation exposure and study characteristics

Table 1 provides the distribution of radiation exposures, average baseline ages and age-adjusted means and per cent characteristics for the sample of men and women who were available for follow-up. The average radiation dose (±SD) for men is 0.41±0.62 and for women 0.36±0.55 ($p<0.001$). For men, 15.3% were exposed to radiation doses ≥1 Gy, while 46.5% were exposed to doses <0.05 Gy. For women, corresponding percents were 11.6% and 44.6%.

After adjusting for differences in baseline age across the ranges of radiation exposure, BMI declined (although modestly) with increased radiation exposure in men ($p=0.016$) but not in women. For women, higher radiation doses were more likely associated with elevated SBP ($p=0.013$). A similar pattern was absent in men. While not significant, T-CHO levels were highest in women who had the greatest dose exposures. For the remaining data, associations with radiation were absent.

Age-adjusted incidence of stroke by radiation exposure

During the course of follow-up, there were 235 haemorrhagic and 607 ischaemic strokes (14.0 and 36.1 per 10 000 person-years, respectively). The average age at the time of a stroke was 73.2 years (range: 43−98 years) for those who were haemorrhagic and 77.0 years (range: 48−100 years) for those who were ischaemic. The average follow-up time before stroke occurrence was 11.1 years (range: 3 months−23 years) for haemorrhagic events and 11.5 years (range: 4 days−23 years) for ischaemic events. There were an additional 84 strokes that were of unknown subtype.

Table 2 provides further details on stroke incidence that was identified according to radiation exposure at the time of bombing. For men, after adjusting for age, the incidence of haemorrhagic stroke rose consistently from 12.2 to 25.2 per 10 000 person-years as radiation exposure increased from <0.05 to ≥2 Gy ($p=0.006$). Risk of haemorrhagic stroke continued to rise with increasing doses <1 Gy ($p=0.006$). For women, differences in the risk of haemorrhagic events were modest for doses <2 Gy but more than tripled when doses went higher ($p=0.002$). There were no significant relationships between radiation and the risk of ischaemic events for either sex (table 2). Relationships to total stroke were largely determined through associations with haemorrhagic events. There were no relationships between radiation and the incidence of strokes that were of unknown origin.

Table 1 Distribution of radiation exposures, average baseline age and age-adjusted means and per cent characteristics for the sample of men and women available for stroke follow-up

	Radiation exposure (Gy)			
Characteristic	<0.05	0.05 to <1	1 to <2	≥2
Men				
Sample size	1539	1266	376	130
Per cent of sample	46.5	38.2	11.4	3.9
Baseline age* (years)	57±13	57±13	54±13	51±11
SBP (mm Hg)	135±24	135±23	133±20	136±19
T-CHO (mmol/l)	4.53±0.88	4.60±0.85	4.65±0.96	4.55±0.96
BMI† (kg/m^2)	21.9±3.0	21.8±3.0	21.7±2.9	21.5±3.0
Diabetes (%)	12.6	14.6	12.5	15.5
In Nagasaki at exposure	40.8	31.1	41.2	30.2
Smoking status (%)				
Past	21.6	21.0	22.7	16.8
Current	66.6	65.6	64.2	68.5
Alcohol intake (%)				
Light (<34 g/day)	44.3	42.0	42.9	44.1
Heavy (≥34 g/day)	38.3	38.3	41.2	38.4
Women				
Sample size	2765	2720	531	188
Per cent of sample	44.6	43.8	8.6	3.0
Baseline age* (years)	59±13	60±13	58±12	56±12
SBP‡ (mm Hg)	134±26	135±26	136±25	137±26
T-CHO§ (mmol/l)	4.94±0.91	5.02±0.96	5.09±1.01	5.15±0.93
BMI (kg/m^2)	22.8±3.6	22.9±3.5	23.0±3.5	22.3±3.2
Diabetes (%)	6.7	8.4	8.0	7.2
In Nagasaki at exposure¶	31.0	26.5	35.7	25.8
Smoking status (%)				
Past	5.1	4.3	5.3	7.2
Current	10.6	14.7	13.8	13.1
Alcohol intake (%)				
Light (<34 g/day)	20.7	21.3	21.3	16.2
Heavy (≥34 g/day)	0.8	1.9	1.3	0.0

Continuous variables are reported as means ± SDs. The remaining variables are reported as per cents.
*Significant decline with radiation exposure (p<0.001).
†Significant decline with radiation exposure (p=0.016).
‡Significant increase with radiation exposure (p=0.013).
§Significant increase with radiation exposure (p<0.001).
¶Significant increase with radiation exposure (p=0.002).
BMI, body mass index; SBP, systolic blood pressure; T-CHO, total cholesterol.

Risk factor-adjusted associations between haemorrhagic stroke and radiation exposure

The association between radiation and haemorrhagic events was further examined after adjustment for age, SBP, BMI, diabetes, T-CHO, cigarette smoking, alcohol drinking and city (table 3). For men, the association was diminished but remained significant (p=0.009). For those exposed to the highest amounts of radiation (≥2 Gy), there was a 2.5-fold excess risk of stroke as compared to doses that were <0.05 Gy (29.1 vs 11.6 per 10 000 person-years). Risk of haemorrhagic stroke also rose with increasing doses <1 Gy (p=0.004), suggesting that the dose−response relationship in men is not entirely attributed to the excess of haemorrhagic events that were observed in the highest ranges of radiation.

For women, while a dose−response relationship across the entire range of radiation and the risk of haemorrhagic events was absent, evidence in table 2 suggests that there may exist a threshold effect. Further analyses identified a significant dose threshold at 1.3 Gy (95% CI 0.5 to 2.3 Gy) where a change occurs in the association between radiation and the risk of haemorrhagic stroke. Below the threshold, risk was unrelated to radiation, while above the threshold, it increased with rising dose. This can better be seen in table 3 for dose strata <0.05, 0.05 to <1.3, 1.3 to <2.2 and ≥2.2 Gy. For doses <1.3 Gy, differences in haemorrhagic risk were modest (14.2 and 13.0 per 10 000 person-years), while it increased to 20.3 per 10 000 person-years for doses that ranged from 1.3 to <2.2 Gy and to 48.6 per 10 000 person-years for doses that were higher. For men, a dose threshold was absent. In both sexes, findings do not appear to be influenced by events that occur at an early age (<55 years).

DISCUSSION

Findings suggest that exposure to increasing radiation doses among atomic bomb survivors beyond a threshold of 1.3 Gy is associated with an increase in the future risk

Table 2 Age-adjusted stroke incidence by radiation exposure

Radiation exposure (Gy)	Sample size	Haemorrhagic		Ischaemic		Total stroke	
		Events	Incidence*	Events	Incidence*	Events	Incidence*
Men							
<0.05	1539	33	12.2	112	40.5	154	56.1
0.05 to <1	1266	37	17.6	81	38.5	132	62.7
1 to <2	376	13	21.4	20	34.9	36	61.9
≥2	130	5	25.2	8	46.3	13	72.4
p Value†			0.006‡		0.788		0.202
Overall	3311	88	15.7	221	39.4	335	59.7
Women							
<0.05	2765	66	13.1	173	34.4	262	52.0
0.05 to <1	2720	63	12.4	174	33.9	264	51.6
1 to <2	531	8	9.3	33	39.8	46	54.9
≥2	188	10	41.9§	6	27.9	19	85.7¶
p Value			0.098		0.930		0.155
Overall	6204	147	13.1	386	34.4	591	52.7

*Incidence rate per 10 000 person-years.
†The p value is a test for trend with dose modelled as a continuous variable.
‡For men, risk of haemorrhagic stroke continued to rise with increasing doses <1 Gy (p=0.006).
§Risk of haemorrhagic stroke in women is higher for doses ≥2 Gy versus lower doses (p=0.002).
¶Risk of total stroke in women is higher for doses ≥2 Gy versus lower doses (p=0.027).

of haemorrhagic stroke in women. While 1.3 Gy is only a point estimate, the lower 95% confidence limit (0.5 to 2.3 Gy) further suggests that there is more than 95% confidence that the true threshold is 0.5 Gy or higher. For men, the incidence of haemorrhagic stroke rose consistently with increasing exposure levels without evidence for a threshold. Even within the dose range <1 Gy, the dose−response observed in men persisted. The 35-year period from the time of the atomic bombing in Hiroshima and Nagasaki to the beginning of stroke follow-up in 1980 may be especially meaningful with regard to the increased use of radiotherapy at younger ages and the increased opportunity for a stroke to develop in later life.[2]

Table 3 Risk factor-adjusted incidence and relative hazards of haemorrhagic stroke by radiation exposure

Radiation exposure (Gy)	Incidence	Relative hazard (95% CI)
Men		
<0.05	11.6	Reference
0.05 to <1	17.7	1.5 (0.8 to 2.7)
1 to <2	20.2	1.7 (0.7 to 4.1)
≥2	29.1	2.5 (0.8 to 7.3)
p Value*	0.009†	
Women		
<0.05	14.2	Reference
0.05 to <1.3	13.0	0.9 (0.6 to 1.4)
1.3 to <2.2	20.3	1.4 (0.6 to 3.7)
≥2.2	48.6	3.5 (1.4 to 9.0)
p Value	0.002	

Incidence rate per 10 000 person-years and relative hazards are adjusted for age, systolic blood pressure, body mass index, diabetes, total cholesterol, cigarette smoking, alcohol drinking and city.
*The p value is a test for trend with dose modelled as a continuous variable. For women, a dose threshold model is used with a dose threshold at 1.3 Gy (95% CI 0.5 to 2.3 Gy).
†For men, risk of haemorrhagic stroke continued to rise with increasing doses <1 Gy (p=0.004).

Patterns of association persisted for the period that predated the 1980 baseline, during a time when enrolment in the AHS continued to be ongoing. For the 1980 baseline used in the current report, >97% of the AHS participants had been enrolled. The 1980 baseline also provides a uniform beginning with a fixed lag time since the bombing of Hiroshima and Nagasaki. More complete data from clinical examinations and a recently conducted mail survey were also available. Although many stroke diagnoses were based on death certificates alone (about 50%), confounding due to changes in the diagnosis of stroke through the advent of neuroimaging in the late 1970s was also thought to be minimised. With regard to the diagnostic uncertainty that is common in any large-scale study, best attempts were made for the proper classification of fatal and non-fatal strokes with the opportunity for adjudication among the study investigators. In the absence of neuroimaging, however, diagnostic limitations are difficult to avoid. In spite of evidence from Japanese samples that suggest that errors in stroke classification could be small,[25 26] subtle distinctions between primary intracerebral haemorrhage and ischaemic events can still exist when neuroimaging is available.

There is also evidence of an excess risk of circulatory disease at low and moderate doses (<5 Gy) in Japanese atomic bomb survivors in the LSS cohort[12] where follow-up began in 1950. Although there were no clinical examinations in the LSS, there was a 9% excess risk of death due to all strokes combined per unit Gy (p=0.02). The 5% excess RR (95%CI −6 to 17) that was observed for cerebral haemorrhage was indistinguishable from a 4% excess RR (−10 to 20) for cerebral infarction.[12] Corroborating evidence also appears elsewhere,[5 10] while reports of uncertainty in the association between radiation and stroke are common,[11 27] most likely due to the extreme difficulties in quantifying radiation exposure in studies that often rely on limited record keeping and historical recall.

Given that the association between radiation and the risk of stroke is plausible, an explanation for the association is far from clear. At high doses (>10 Gy), there is well-established evidence from radiotherapy patients of direct damage in circulatory systems, predominantly the consequence of excessive cell killing and the associated response to cell damage. In contrast, epidemiological studies suggest that the mechanisms associated with low- and moderate-dose ionising radiation (<5 Gy) are different.[16–18] More direct mechanistic derangements that might explain an association with haemorrhagic stroke include fibrinoid necrosis of the small arteries and arteriole, a common underlying cause for intracerebral haemorrhage due to hypertension in murine brain[28] or arteriovenous malformations in humans.[29] Fibrinoid necrosis in vessels is also preceded by proinflammatory cytokines and observed in late cerebral radionecrosis at radiotherapy doses <0.05 Gy.[30] Elevated blood pressure,[19] hypertension[31] and inflammation (C reactive protein and interleukin-6) among the atomic bomb survivors[32 33] might further promote a fibrinoid necrosis link with haemorrhagic stroke. Hypertension has a greater impact on haemorrhagic stroke incidence than cerebral infarction.[34] In the absence of a clear explanation for the reported findings, further study of subclinical arteriosclerosis or biological evidences among the AHS may provide additional insight into the role that radiation has on promoting stroke and its subtypes.

In the current report, several notable limitations need to be addressed. Whether findings apply to other ethnicities is unknown. Genetic susceptibilities may be different. The number of haemorrhagic events is also limited and too insufficient to allow for a careful assessment of the effect of radiation on the risk of stroke between risk factor strata. In spite of the limitations, findings from the AHS warrant consideration and further study. Attractive features include the high rate of participation between examination cycles and free access to standardised medical care and evaluation. Measurement of radiation exposure also adheres to a rigorous system of quantification.[14] Among large cohort studies, the dosimetry in the AHS is unusually precise. In conclusion, the risk of haemorrhagic stroke increases with rising radiation exposure for both sexes. In men, it seems to occur across the full range of radiation exposures, while in women, the risk becomes apparent when doses exceed a threshold at about 1.3 Gy. Given the observed latency between radiation exposure and haemorrhagic stroke in the current study, a consequence of the expanded use of radiotherapy in younger individuals[2] could be an increased opportunity for the development of adverse outcomes in later life.

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Contributors IT contributed to the study design, interpreted the data and took the lead in writing the paper. RDA conducted the statistical analyses, interpreted the data and made substantial contributions to drafting the methods and results sections of the paper. TO and TT played a lead role in data acquisition. They also contributed to the study design and in writing the paper. KO, MA and SF had important roles in data interpretation, in writing and reviewing the paper and provided essential oversight and supervision of the study design. KK and MM assisted in writing and supervision of the final draft of the paper. Their oversight of the final product for verification of the study findings was essential. Credit for all authors is based on (1) substantial contributions to conception and design (IT, RDA, TO, TT, KO, MA, SF), acquisition of data (TO, TT) or analysis and interpretation of data (IT, RDA, TO, TT, KO, MA, SF, KK, MM); (2) drafting the article or revising it critically for important intellectual content (all authors) and (3) final approval of the version to be published (all authors). Each author participated sufficiently in the work and accepts public responsibility for appropriate portions of the content in which they have an expertise. All authors critically revised the manuscript for important intellectual content.

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