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Research article

The ST segment depression pattern in asymptomatic peri-menopausal female athletes

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ABSTRACT

Background: ST segment has not been well investigated in asymptomatic peri-menopausal female athletes, when the CV risk is higher.
Aims: The aims of the study is to investigate the prevalence of ST segment depression in peri-menopausal female athletes, divided in four age groups.
Methods: in a cohort of 6010 female athletes aged 45–65 years old, 161 subjects were selected for the presence of ST segment depression, revealed by maximal ergometric test. All athletes were also evaluated by physical examination and echocardiography. Inclusion criteria for ST segment depression were ST depression >0.5 mm respect to baseline and its depth was divided in 0.5 mm, 0.5–1 mm, 1–2 mm categories. Its behavior was classified in ascending, horizontal and descending and it was studied in relation to the age range (<51; 51–55; 56–60; >60).
Results: ST segment depression was mainly evident in inferolateral leads in all groups (63%, 70,3%, 71%, 63,6%, for <51; 51–55, 56–60 and 61–65 respectively) with horizontal pattern (52,2%, 59,5%, 57,8%, 63,6%) and 1–2 mm depth (43,5%, 46,7%, 60,6%), with the exception of the range 51–55, mainly showing a depth of 0,5-1 mm (45,9%). The older group showed increased SBP (137.5 mmHg, p = 0.007) and BMI (24.3, p = 0.093) values. Mitral prolapse was shown in 11,8% while 36,6% showed systolic flattening of mitral leaflets.
Conclusions: ST depression in asymptomatic menopausal female athletes is frequent and it is characterized by a specific presentation pattern. This is particularly important in the menopausal age when CV risk factors are more prevalent.

1. Introduction

The ergometric maximal test (EMT) is the most important clinical non-invasive tool to investigate coronary reserve and cardiac electrical function especially for those subjects suspected of having coronary artery disease (CAD) [1]. Particularly, ST segment analysis during exercise testing is largely considered to eventually discover myocardial ischemia in asymptomatic and before the clinical appearance [2]. According to meta-analyses and multicenter databases, the diagnostic accuracy of the traditional ST-segment slope as depression especially in women and during exercise, is however limited. The mean sensitivity was proven to be around 61% and the mean specificity is 70%, markedly lower than in men, positioned at 68% and 77%, respectively [3, 4, 5]. Multiple gender factors can cause differences in the EKG interpretation between men and women. First of all, female thoracic conformation often limits the standard EKG leads position in women. This aspect can potentially create confusion, inducing a wrong pathological clinical interpretation of the recorded EKG. In addition, the impact of hormonal balance in the EKG pattern between men and women [6] can add other modifications in the EKG morphology. It has been demonstrated that a different EKG recorded can be characterized by diverse pattern in different phases of menstrual cycle in the same woman, despite any clinical relevance. The same behavior is not described in men [7]. In addition, other studies showed that ST pattern in women changed with age: progressive loss of estrogens with reciprocal increase in androgens and progesterone with aging is related to ST segment pattern changes [8, 9]. Considering all the previous described aspects and particularly the relevance of the progressive increase in cardiovascular age-related risk, the evaluation of the

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combination of these components in the EKG modification is relevant, particularly among active women [10]. Especially menopause has been widely considered a crucial period for the potential higher rate of cardiac events. No data are anyway available about any specific EKG different patter among diverse age time in active women. The first aim of the study is to investigate the prevalence of asymptomatic ST-segment depression on the bases of three different parameters (depth, leads, pattern) evaluated in the exercise test in a cohort of perimenopausal active regularly trained women, practicing different sport disciplines. The second aim is to evaluate the possible correlation of the single patterns to cardiovascular risk factors such as age, body mass index (BMI), blood pressure levels and the main systolic and diastolic echocardiographic parameters.

2. Methods

2.1. Investigated subjects

Since 2000 up to 2019, a large cohort of 6010 female athletes, in the perimenopausal-menopausal period (aged 45–65 years old), practicing different sport disciplines (45% running, 27% swimming, 14% tennis, 10% dancing, 2% cycling, 1.5% volleyball, 0.5% other sports) and has been evaluated for the eligibility at the Sport and Exercise Medical Centre in Careggi Hospital, Florence. A subgroup of 161 completely asymptomatic subjects was selected for the presence of ST segment depression detected at maximal ergometric test (EMT). Exclusion criteria were out of the age range (<45 or >65 years), presence of symptoms, as chest pain or palpitation or syncope or history compatible with ischemic heart disease at baseline, and any eventual drug assumption. All the athletes were therefore evaluated by physical examination and personal and familiar history and in addition by an 2D echocardiographic exam, at rest condition, to exclude any structural cardiomyopathy.

All subjects gave their informed consent before eligibility procedure. Local ethics committee of the Azienda Ospedaliero Universitaria Careggi, Florence (AOUC), University of Florence approved the retrospective data collection and analysis conducted in accordance with the Declaration of Helsinki.

2.2. EKG and exercise testing pattern

Study participants underwent to maximal exercise testing, performed by treadmill (Bruce protocol, Esaote My Formul@, Florence and Genova, Italy) or by cycle ergometer (increasing load of 25 Watts every 2 min; Cosmed Quark CPET, Rome Italy). As normally requested to obtain the certification for eligibility, the target maximal heart rate (HR) was defined as achievement of ≥85% of maximal predicted HR for age calculated as 220 – age (in years). Blood pressure (BP) measurements were taken at rest, at the peak of the exercise and at the 3^{rd} minute of recovery. Patients were seated comfortably in a quiet environment for 5 min before beginning resting BP measurements. Three BP measurements were recorded, 1–2 min apart, and additional measurements were recorded only if the first two readings differed by > 10 mmHg. BP was also measured in both arms at the first visit to detect possible between-arm differences. BP was recorded as the average of the last two BP readings. A standard bladder cuff (12–13 cm wide and 35 cm long), positioned at the level of the heart, was used [11].

The exercise tests were sign- and symptom-limited maximal tests using the recommended criteria for termination [12].

EMT was terminated after 4 min of recovery. This is a normal procedure in absence of alterations.

Following the ACCF/AHA and ACSM consensus conference guidelines [13, 14] a positive or suspected exercise test for ischemia was defined as ST segment depression >0,5 mm in 2 contiguous leads at any time during exercise that persisted for ≥3 beats. The ST segment was defined from the J point to 0.08 ms after the J point. The ST segment was compared with the PR segment to determine amplitude of deviation. The different ST segment depression was studied with respect of the age range (<51; 51–55; 56–60; >60). The ST segment behavior was also classified in ascending, horizontal and descending; it was divided in three categories due to its amplitude (0.5–1 mm; 1–2 mm; >2 mm). The depression and the behaviour were calculated using the included software; it was further evaluated in terms of relationship to the segmental 12 EKG leads pattern: in inferior leads (DII-III, aVF), lateral leads (V5-6), infero-lateral leads, anterior leads (V3-4) or anterolateral leads. A possible correlation between ST segment pattern and other parameters was also analyzed. From the echocardiographic exam some parameters as interventricular septum (IVS) and posterior wall thickness (PWT), left ventricular end-diastolic and end-systolic diameters (LVEDD and LVESD), ejection fraction (EF), diastolic function assessed by E/A were obtained. Any eventual mild valve dysfunction associated, as mitral prolapse or stenosis were considered in the multivariate analysis and classified following the ASE 2017 guidelines [15]. Among the hemodynamics parameters, the systolic and diastolic pressure (SPB and DBP) expressed in mmHg were measured at baseline, at the apex of the exercise test and during the recovery. Particularly, the normalization of ST depression during exercise testing and at the recovery was observed. Finally, as suggested by literature [17] a possible correlation between ST depression and BMI was considered.

2.3. Statistical analysis

Descriptive statistical analysis, Kruskal-Wallis test and X2 test for comparisons among age groups were performed using IBM-SPSS® version 25.0 (IBM Corp., Armonk, NY, USA, 2017) Statistical significance was set at $p \leq 0.05$ and all p values were two-sided.

3. Results

3.1. General data

The total investigated population was composed of 6010 women aged 45–65 years old. The prevalence of ST segment depression in the general population was 2.7%, corresponding to 161 women. Mean age of the latter was 54.98 ± 6,14 years old; patients with ST segment depression were divided into 4 age ranges (45–50; 51–55; 56–60; 61–65): the range 45–50 was composed of 46 subjects (29%), range 51–55 was composed of 37 subjects (23%), range 56–60 was composed of 45 subjects (28%) and range 61–65 was composed of 33 subjects (20%).

On an overall analysis, ST segment depression was more often represented in inferolateral leads in all the age groups, with horizontal pattern and 1–2 mm depth, with the exception of the age 51–55 years old, where 0,5-1 mm was the most frequent depth found (Table 4). More specifically, the age range 45–50 showed ST segment depression in inferolateral leads in 63% with horizontal pattern in 52,2% and 1–2 mm depth in 43,5%. The age range 51–55 showed ST segment depression in inferolateral leads in 70,3% with horizontal pattern in 59,5% and 0,5-1 mm depth in 45,9%. The age range 55–60 showed ST segment depression in inferolateral leads in 71,1% with horizontal pattern in 57,8% and 1–2 mm depth in 46,7%. Finally, the age range 61–65 showed ST segment depression in inferolateral leads in 63,6% with horizontal pattern in 63,6% and 1–2 mm depth in 60,6% (Table 1).

ST segment depression was detected mainly in inferior and inferolateral leads in the range of 56–60 age (37.5 and 29.6%), while the lateral and anterior leads in <51 age group (35.3 and 66.7%) and the anterolateral leads in 51–55 age group (44,4%) were lower involved. Ascending and descending ST segment depression were mainly present in <51 age group (31.3% and 50% respectively), while horizontal pattern was more present in 56–60 age group (28%). <51 age group showed the lowest depth of ST segment depression (<0.5 mm, 42.9%) while 0.5–1 mm and 1.0–2.0 mm depth was mainly present in 56–60 age group (31.3 and 27.6% respectively).

Most of the ST segment depression found during EMT normalized during the recovery (78.9%), with no differences among the groups, as

Table 1. Table shows the distribution of ST segment depression and its pattern in every age range, respectively considering the leads involved, the type and the depth. The figures inside the table correspond to the number of subjects in every subgroup and its percentage (N (%)).

Age	EKG Leads					Type			Depth (mm)		
	Inf	Lat	InfLat	Ant	AntLat	Asc	Hor	Desc	<0.5	0.5–1.0	1.0–2.0
<51	6 (13.0)	6 (13.0)	29(63.0)	2 (4.3)	3 (6.5)	20 (43.5)	24(52.2)	2 (4.3)	9 (19.6)	17 (37.0)	20(43.5)
51–55	4 (10.8)	3 (8.1)	26(70.3)	0 (0.0)	4 (10.8)	14 (37.8)	22(59.5)	1 (2.7)	5 (13.5)	17(45.9)	15 (40.5)
56–60	9 (20.0)	4 (8.9)	32(71.1)	0 (0.0)	00 (0,0)	18 (40.0)	26(57.8)	1 (2.2)	4 (8.9)	20 (44.4)	21(46.7)
>60	5 (15.2)	4 (12.1)	21(63.6)	1 (3.0)	2 (6,1)	12 (36.4)	21(63.6)	0 (0.0)	3 (9.1)	10 (30.3)	20(60.6)
Total N (%)	24 (14.9)	17 (10.6)	108 (67.1)	3 (1.9)	9 (5.6)	54 (39.7)	93 (57.8)	4 (2.5)	21 (13.0)	64 (39.8)	76 (47.2)

Legend: Inf = Inferior, Lat = Lateral, InfLat = Inferolateral; Ant = Anterior, AntLat = Anterolateral; Asc = Ascending, Hor = Horizontal, Desc = Descending.

shown in Table 2. Normalization occurred in the first 2 min of recovery. As specified above, none of the patients was found to have cardiopathies or ischemic conditions even if ST segment depression did not disappear at rest.

Blood pressure values found at the EMT, SBP and DBP were normal in all groups with the exception of the older group where a significant increase in SBP (137.5 ± 19.6 mmHg, $p = 0.007$) but not in DBP (79.7 ± 10.8 mmHg $p = 0.880$) was shown at the baseline of ergometric test (Table 2).

The older group also showed a mild increase in BMI, although still within normal range (24.3). Mean values for global BMI in the population was normal (Table 3).

Echocardiographic parameters, contractile function evaluated by ejection fraction (EF) estimated following the Simpson's rule method [14] and diastolic function, evaluated by E/A, were within normal range in all groups (Table 3); left ventricular wall thicknesses (IVS and PWT) and LV diameters (LVEDD and LVESD) were normal as well (Table 4). Only a small percentage of the studied population showed a mild increase in parietal thickness, especially in the older group (6.1% for IVS and 9.1% for PWT), although without statistical significance.

A possible relationship between ST segment depression and specific cardiac morphologic patterns, compatible with eligibility, was investigated.

Mitral prolapse, which was initially assessed, was found in 11.8% of the investigated population while only 2.5% of the population showed mitral stenosis (Table 5).

Interestingly, 36.6% of the population showed systolic flattening of mitral leaflets, associated to a mild depression of ST segment.

4. Discussion

Peri-menopausal time represents a critical period where the potential EKG alteration can induce to suspect myocardial damage despite the absence of specific symptoms. In particular, the presence of ST depression at the EMT, if not correctly evaluated, can be associated to a potential reduction in coronary reserve. Especially in females, as a consequence of the thorax shape, the interpretation of the EKG can induce an incorrect understanding. This is particularly evident when the depression occurs after exercise test.

The main results of our study show the specific presentation pattern of ST segment depression in perimenopausal women.

In our study, only a small subgroup (2.7%) of asymptomatic, peri-menopausal women, showed an exercise EKG ST segment depression. Our data are in accordance with other previous studies [17, 18] where it was reported an incidence in ST segment depression during EMT around 6.2% and 4.7%. This apparent low incidence could be firstly attributed to the investigated population, in a range of age, younger if compared to the menopausal period and normally associated to a higher level of estrogen hormones, which play a protective role. This female transition time, despite physically activity, seems to be important for the evolution of the EKG pattern particularly in terms of ST depression.

The false positive EKG pattern in women at peri-menopausal and menopausal time, as well the accuracy of exercise electrocardiography in the interpretation of the ST segment responses have been largely discussed. In addition, literature has payed attention to the role of the estrogens, even if in oral therapy [19] in the EKG abnormal pattern. This aspect could partially justify the low percentage of ST depression in our population, which is in addition particularly active.

A special attention has been made to the principal leads involved for this peculiar pattern. From our data the prevalent ST segment depression was represented in inferolateral leads in all the age groups, with horizontal pattern and 1–2 mm depth, with the exception of the age 51–55 years old, where 0,5-1 mm was the most frequent depth found. This is consistent with the involvement of right coronary artery (RCA) for inferior leads while the left anterior descending coronary artery (LCA) is in accordance to lateral leads.

It has been demonstrated, as in case of coronary occlusion in >45 years old women, a prevalent involvement of LCA (52%) if compared to the RCA (30%). In women with one vessel disease the prevalent involvement is of LCA (64%), while RCA was occluded in 29% [20].

Left circumflex artery was involved in 18% and 8% respectively. Furthermore, it has been reported that multivessel disease was more prevalent in older women compared to pre-menopausal women [21]. These data seem to support our findings.

Literature reports that the horizontal pattern is the most frequently found and is usually associated with microvascular angina [22] without any evidence at the morphological study as in case of echocardiographic evaluation.

Table 2. Percentage of ST depression normalization during the recovery of exercise maximal test and blood pressure behavior during exercise maximal test.

Age	Recovery normalization - N (%)		DBP baseline	SPB baseline	DBP apex	SBP apex	DBP rec	SBP rec
	No	Yes	Mean ± SD					
<51	10 (21.7)	36 (78.3)	78.3 ± 11.9	122.8 ± 15.6	76.6 ± 14.2	160.2 ± 22.7	73.9 ± 11.6	121.4 ± 16.3
51–55	9 (24.3)	28 (75.7)	79.2 ± 9.0	126.8 ± 13.2	79.31 ± 17.2	174.7 ± 24.5	75.1 ± 9.9	125.9 ± 14.9
56–60	9 (20.0)	36 (80.0)	79.9 ± 8.2	127.3 ± 16.3	78.9 ± 15.5	171.4 ± 24.5	89.1 ± 93.5	129.1 ± 17.2
61–65	6 (18.2)	27 (81.8)	79.7 ± 10.8	137.5 ± 19.6	81.7 ± 16.1	171.3 ± 24.7	76.9 ± 12.2	139.7 ± 25.7
Total	34 (21.1)	127 (78.9)	79.2 ± 10.1	128.2 ± 17.0	78.9 ± 15.6	168.9 ± 24.5	79.1 ± 50.7	128.3 ± 19.4

DBP = diastolic blood pressure, SBP = systolic blood pressure.

Table 3

Age		BMI	EF	E/A					Total
					<0.75	0.75–1.5	1.5–2.0	>2.0	
<51	Mean ± SD	22.2 ± 2.8	61.9 ± 6.9	N (%)	0 (0.0)	11 (23.9)	30 (65.2)	5 (10.9)	100.0%
51–55	Mean ± SD	22.0 ± 6.5	63.0 ± 5.3	N (%)	0 (0.0)	9 (24.3)	27 (73.0)	1 (2.7)	100.0%
56–60	Mean ± SD	22.6 ± 3.3	63.1 ± 3.9	N (%)	1 (2.2)	19 (42.2)	25 (55.6)	0 (0.0)	100.0%
61–65	Mean ± SD	24.3 ± 3.4	62.2 ± 5.8	N (%)	0 (0.0)	18 (54.5)	15 (45.5)	0 (0.0)	100.0%
Total	Mean ± SD	22.8 ± 4.1	62.5 ± 5.6	N (%)	1 (0.6)	57 (35.4)	97 (60.2)	6 (3.7)	161 (100.0)

Table 4

Age	IVST (mm)				PWT (mm)				LVEDD (mm)			LVESD (mm)		
	<7	7–9	9–11	>11	<7	7–9	9–11	>11	<38	38–52	>52	<21	21–38	>38
<51	1 (2.2)	30(65.2%)	14 (30.4)	1 (2.2)	3 (6.5)	30(65.2)	12 (26.1)	1 (2.2)	0 (0.0)	42(91.3)	4 (8.7)	0 (0.0)	42(91.3)	4 (8.7)
51–55	0 (0.0)	28(75.7)	9 (24.3)	0 (0.0)	0 (0.0)	25(67.6)	12 (32.4)	0 (0.0)	0 (0.0)	33(89.2)	4 (10.8)	1 (2.7)	34(91.9)	2 (5.4)
56–60	2 (4.4)	30(66.7)	13 (28.9)	0 (0.0)	2 (4.4)	26(57.8)	17 (37.8)	0 (0.0)	0 (0.0)	44(97.8)	1 (2.2)	0 (0.0)	44(97.8)	1 (2.2)
61–65	0 (0.0)	18(54.5)	13 (39.4)	2 (6.1)	0 (0.0)	18(54.5)	12 (36.4)	3 (9.1)	0 (0.0)	32(97.0)	1 (3.0)	1 (3.0)	32(97.0)	0 (0.0)
Total	3 (1.9)	106 (65.8)	49 (30.4)	3 (1.9)	5 (3.1)	99 (61.5)	53 (32.9)	4 (2.5)	0 (0.0)	151 (93.8)	10 (6.2)	2 (1.2)	152 (94.4)	7 (4.3)

Table 5

Age		Mitral prolapse		Systolic flattening		Mitral stenosis		Total
		No	Yes	No	Yes	No	Yes	
<51	N (%)	38 (82.6)	8 (17.4)	29 (63)	17 (37)	44 (95.7)	2 (4.3)	46 (100)
51–55	N (%)	33 (89.2)	4 (10.8)	23 (63.9)	13 (36.1)	37 (100)	0 (0.0)	37 (100)
56–60	N (%)	42 (93.3)	3 (6.7)	30 (66.7)	15 (33.3)	45 (100)	0 (0.0)	45 (100)
61–65	N (%)	29 (87.9)	4 (12.1)	20 (60.6)	13 (39.4)	31 (93.9)	2 (6.1)	33 (100)
Total	N (%)	142 (88.2)	19(11.8)	102 (63.8)	58(36.3)	157 (97.5)	4(2.5)	161 (100)

Conversely, in three of the investigated age groups, an ST depth between 1 and 2 mm was found. Authors address these findings to a high probability of coronary artery disease [23]. This pattern has been also found in our study and in the majority of our patients. A normal echocardiogram excluded any structured cardiac disease, supporting the theory of a microangiopathic involvement, not detectable by standard 2D echocardiography. Our female athletes did not undergo to additional exams, since the tests performed were not sufficiently positive and all of them were asymptomatic. Furthermore, others exams, such as stress echocardiography and myocardial SPECT are normally beyond the field of action of Sport Medicine, and they are performed just in case of real suspicion of coronary artery disease. For this reason, they have not been considered in the present study.

4.1. Recovery normalization

78.9% of the enrolled patients showed a normalization of ST segment depression during the first recovery of EMT. This data should confirm that ST segment alteration found in our patients was still not clinically significant. This is also confirmed in a study by Chow et al: the results of their study indicate that among patients with an electrically positive EMT, recovery of ST segment depression within 1 min was associated with a significantly less ischemic burden on subsequent myocardial perfusion imaging [24].

Blood pressure values at EMT were normal with exception of the >60 years old group where a significant increase in SBP was shown if compared to the rest condition, however within the normal range of values. This finding was not associated with a difference in ST segment behavior during EMT, but it could reflect the major prevalence of augmented vessels resistance in older people.

It is well known as the obesity and overweight conditions are often associated with increased cardiovascular disease (CVD) risk [25], particularly higher trunk fat is associated with increased risk of CVD while higher leg fat was associated with decreased risk of CVD [16]. In our study no specific relationship between the ST pattern and the body composition was found due to the fact the investigated athletes had a normal body mass index and the Waist and hip circumferences were not measured in our patients.

In terms of echocardiographic investigation, some attentions have been payed to the possible association between ST depression and mitral valve abnormalities.

Literature reports some data about the association between mitral prolapse and repolarization abnormalities. Particularly, mitral valve prolapse seems to be associated to the ST segment depression and mainly in inferolateral leads. This relation seemed more relevant in asymptomatic patients than for symptomatic [26]. The percentage of an effective MVP found in our study is low and around 11.8%.

Interestingly, 36.6% of the population showed systolic flattening of mitral leaflets associated toa mild depression of ST segment. The consequential relation between these mitral characteristics has not been investigated yet. A possible explanation could be the effect of mitral leaflets movement during systole: the leaflets flattening could strain/stretch the parietal walls close to the mitral anulus, which could result in a blood flow reduction in the area. The effect of this mechanism could be recorded by EKG leads as a transient ischemic event. Further investigations would help to understand this phenomenon.

5. Limits of the study

The study presents anyway some limits. The investigated population is restricted to athletes and sedentary people have not been involved in the study. In addition, some anthropometric parameters are missing as well as the hormonal status for a complete investigation. The assumption of estrogens or progestins as a substitutive therapy during menopause could have an important correlation with the data found despite the well known protective effect of the estrogens supplement toward CV events.

The study does not include information about any possible additional exams related to a potential diagnosis of coronary artery disease. In any case to our knowledge, none of them reported cardiac events.

6. Conclusions

ST depression in asymptomatic menopausal female athletes is more frequent than previously observed and shows a specific presentation pattern. This aspect is crucial in the menopausal age when CV risk factors like an abnormal SBP behavior or overweight are more prevalent. For this reason, it is very important, especially in sports medicine, to highlight historical symptoms and pay attention to the eventual additional exams to detect the presence of CAD, that cannot be excluded in other ways.

The study also supports the hypothesis of a heterogeneous behaviour of the ST pattern at the EKG interpretation, particularly in this specific female transition period between the peri-menopausal towards menopausal time [27]. The peculiarity of the present investigation is that the studied population is composed of athletes, so it seems reasonable to support the hypothesis that sport is not sufficiently protective for this aspect. Further investigation will be necessary to detect the eventual impact of moderate physical activity in the reduction of the ST depression.

The complete absence of symptoms of the investigated subjects, and in parallel the ST segment depression during EMT seems to be related to menopause – perimenopause time rather than to an ischemic condition. The reported data are in agreement with current literature [28].

Declarations

Author contribution statement

Melissa O., G. Orlandi and L. Stefani: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

V. Bini, C. Fiorillo and M. Becatti: Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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