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Risk prediction for advanced neoplasia using longitudinal adherence measures to fecal immunochemical test-based colorectal cancer screening programs

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ABSTRACT

Background: Patterns of longitudinal adherence may predict advanced neoplasia (AN) detection in subsequent rounds of colorectal cancer (CRC) screening. However, after more than five rounds, it is important to obtain a simplified measure. The aim was to determine the best simplified measure of longitudinal adherence to predict AN detection in CRC screening.

Methods: Individuals with four invitations from a Dutch Fecal immunochemical testing (FIT-)based pilot study and two Italian FIT-based CRC screening programs were included. We calculated AN detection in the fourth round, stratified by prior adherence. Five simplified measures were compared to full information (permutations) using chi-squared goodness-of-fit: adherence previous invitation, consistency, frequency, frequency + adherence previous invitation, and proportion of invitations covered.

Results: AN detection in the fourth round was highly dependent on prior adherence behavior. For inconsistent adherence, detection in the fourth round was strongly dependent on frequency and time since last participation. The performance of the simplified measures to capture this variation differed considerably. 'Adherence previous invitation' scored worst in predicting AN detection. 'Frequency+adherence previous invitation' had lowest chi-squared goodness-of-fit.

Discussion: The simplified measure 'frequency+adherence previous invitation' is the best measure to reflect patterns of longitudinal adherence and could be used to emphasize to individuals the importance of CRC screening.

1. Introduction

Colorectal cancer (CRC) screening is an effective way to reduce CRC incidence and mortality.(Cardoso et al., 2021; Lauby-Secretan et al., 2018) Multiple modalities have been recommended for screening, such as fecal immunochemical testing (FIT) and endoscopy (colonoscopy or sigmoidoscopy), which differ in invasiveness and advanced neoplasia (AN) detection. The effectiveness of a screening program is strongly dependent on the adherence and guidelines recommend minimal adherence standard of 45% in each single round.(Segnan et al., 2010) However, while the benefit of endoscopy can be ensured performing the test every 10 years, or even once in a lifetime, FIT screening requires repeat screening (i.e. annual or biennial) and therefore repeated adherence over several rounds, to achieve the expected protective effect. Thus measures of individuals' longitudinal adherence are needed to compare the expected health impact and effectiveness of different programs and to monitor their performance.(Toes-Zoutendijk et al., 2017).

Several reports of screening activity are already presenting the

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; AN, advanced neoplasia; μg Hb/g, microgram Hemoglobin per gram.

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results of performance indicators stratified by previous adherence, usually using two levels (attenders versus non-attenders in previous rounds), which show a different response in adenoma detection rate. (Garcia et al., 2012; Lo et al., 2015; Senore et al., 2019; Zorzi et al., 2015)This approach does not however account for the variability in the adherence behavior of the individuals in the target population, which may result in several different adherence patterns, showing a different predictive value for screening outcomes in subsequent screening rounds.

Ideally, longitudinal adherence could be accurately described by considering all possible combinations of adherence to multiple screening rounds. In practice, the number of screening rounds varies between 11 and 13 in the majority of FIT-based programs, and can be as high as 25 and the number of combinations grows exponentially with the number of rounds (e.g. 2^5 = 32 possible combinations for five rounds. Therefore, as long as patterns of longitudinal adherence can predict future screening behavior and outcomes, it is important to obtain a simplified measure, that accurately reflects those patterns by their impact on participation and yield in subsequent screening rounds.

Previous studies identified possible metrics for longitudinal adherence, but they were never systematically evaluated using real-world data from (ongoing) CRC screening programs with multiple screening rounds.(Doria-Rose et al., 2021) Therefore, the aim of this study was to use real-time data to compare multiple measures of longitudinal adherence and determine the best simplified measure to predict the participation rate, positivity rate and detection rate of AN in a subsequent screening round in FIT-based CRC screening programs.

2. Material and methods

2.1. Dutch trial and Italian program

We used data of a randomized population-based trial in the Netherlands and the population-based organized screening programs of the Piedmont region and of the Reggio Emilia province in Italy. Details about the trial and Italian program can be found in Table 1 and in previous publications (Hol et al., 2010; Kapidzic et al., 2014; Senore et al., 2020; van der Vlugt et al., 2017; van Roon et al., 2011; van Roon et al., 2013). Data for both the trial and the Italian programs included date of invitation, participation, FIT result, participation to follow-up colonoscopy, and the detection of AN. In this study, we used closed cohorts in which only individuals who were invited for four screening rounds and did not have a positive FIT result in previous three rounds were included. Ethical approval was not needed for this study.

Table 1
Screening programs including their overall distribution of adherence patterns.

	Dutch trial		Piedmont		Reggio Emilia	
Screening modality	Biennial one-sample FIT		Biennial one-sample FIT		Biennial one-sample FIT	
Screening age, years	50–74		59–69		50–69	
FIT cut-off	10 μg Hb/g feces		20 μg Hb/g feces		20 μg Hb/g feces	
Permutations*	*N*	%	*N*	%	*N*	%
0000	2888	25.0%	47,175	40.8%	17,030	23.2%
0010	187	1.6%	2083	1.8%	1050	1.4%
0100	88	0.8%	1974	1.7%	1198	1.6%
1000	190	1.6%	2923	2.5%	1684	2.3%
0001	470	4.1%	4034	3.5%	1420	1.9%
0110	105	0.9%	1284	1.1%	684	0.9%
1010	94	0.8%	845	0.7%	573	0.8%
1100	86	0.7%	1762	1.5%	997	1.4%
1001	108	0.9%	962	0.8%	577	0.8%
0011	514	4.4%	3213	2.8%	1556	2.1%
0101	92	0.8%	1207	1.0%	707	1.0%
1110	266	2.3%	4210	3.6%	2043	2.8%
0111	733	6.3%	7279	6.3%	3659	5.0%
1011	319	2.8%	1806	1.6%	1578	2.1%
1101	141	1.2%	1656	1.4%	1258	1.7%
1111	5293	45.7%	33,280	28.8%	37,390	50.9%

Abbreviations: FIT, fecal immunochemical test; μg Hb/g, microgram Hemoglobin per gram.
* 0's and 1's designate participation in prior rounds. E.g. 0000 = no participation in any of the rounds. 1100 = participation in rounds 1 and 2 and no participation in rounds 3 and 4.

2.2. Measures of longitudinal adherence

2.2.1. Permutations – comparator using full information

This measure distinguishes between all possible patterns of adherence over multiple screening rounds. In case of *n* screening rounds, the number of possible adherence schemes (i.e. permutations) equals 2^n. For example, in case of two screening rounds, there are $2^2 = 4$ adherence patterns; (1) the individual attended in both screening rounds (11), or (2) the individual only attended in the first screening round (10), or (3) the individual only attended in the second screening round (01), and (4) the individual did not attend in any screening round (00). This measure captures all information with respect to screening adherence and serves as the comparator measure for the other measures.

2.2.2. Adherence previous invitation measure

A measure that only indicates whether the individual attended in their previous invitation. 'Yes' indicates that they have attended in their previous invitation, and 'No' indicates that they have not attended in their last invited screening round.

2.2.3. Consistency measure

Individuals are classified into three different groups; individuals attended (1) consistently, (2) inconsistently, and (3) never. Consistent individuals attended in all three prior screening, inconsistent individuals, attended in some but not all screening rounds, and the last group never attended in any screening round.

2.2.4. Frequency measure

'Frequency' indicates how many times an individual attended in the screening rounds for which this individual was invited.

2.2.5. Frequency + previous invitation measure

'Frequency + previous invitation' adds, besides frequency, information that indicates whether the individual attended in their previous screening round. To clarify, individuals obtain an additional binary value, 0 indicating that they did not attend in the previous round, and 1 indicating that they did. For example, '2,1' indicates that this individuals attended twice, one of them was their last invitation.

2.2.6. Proportion of invitations covered

The 'proportion of invitations covered' is defined by the total number of times attended in the cohort divided by the total number of invitations in the cohort. We identified four categories: 0.00, 0.01–0.50, 0.51–0.99, and 1.00.

2.3. Outcomes and analysis

For both the Dutch trial and the Italian program, the absolute and relative number of individuals that attended according to the possible permutation pattern over four screening rounds were evaluated (Table 1). Next, all possible permutations for the first three screening rounds were considered and the observed participation rate, positivity rate and detection rate of AN in the fourth screening round were calculated for each permutation. The same was done for all simplified measures. The predictive performance of the measures was evaluated by comparing the predicted outcomes of the simplified measures with those of the corresponding permutations using the chi-squared deviance. (Plackett, 1983) The simplified measure with the smallest deviance for

all screening outcomes was considered best. The analyses were performed using R 4.1.2..

2.4. Validation

We validated our results using five screening rounds from the two Italian regions. All six measures of longitudinal adherence were computed over four screening rounds and based on these, we estimated participation, FIT positivity and detection of AN in the fifth screening round. Again, chi-squared deviance was used to determine the best predicting measure.

3. Results

3.1. Comparator: Permutations in relation to detection rate AN fourth round

Detection rate of AN per 1000 individuals in the fourth screening round of individuals who did not previously attend (000) was 5.1 in the Dutch trial, 3.4 in Piedmont and 3.0 in Reggio Emilia (Table 2). Detection rate of AN in the fourth screening round for individuals who attended once (100,010,001) varied between 2.3 and 4.6 in the Dutch Trial, between 1.5 and 2.4 in Piedmont and 0.9–1.5 in Reggio Emilia. For individuals who attended twice (011,110,101), the detection rate of AN in the fourth screening round varied between 1.6 and 2.1 in the Dutch trial, between 1.3 and 1.7 in Piedmont and between 1.0 and 1.5 in Reggio Emilia. The detection rate of AN for consistent individuals (111) was 0.015, 1.0 and 1.0, in the respective areas. Similar to detection rate of AN, participation and positivity rate in the fourth screening round was dependent on frequency and recency of prior adherence (Table 2).

3.2. Estimates of the simplified adherence measures

Fig. 1 shows the predictions for detection rate of AN per 1000 individuals for the worst (adherence previous invitation) and the best (frequency + adherence previous invitation) of the simplified measures compared to the corresponding permutations. Supplementary Fig. S1a, b, and c show the predictions for participation, positivity rate per 100 individuals and detection rate of AN per 1000 individuals for all other simplified measures. The simplified measure 'adherence previous invitation' estimated detection rate of AN per 1000 individuals in the fourth screening round to be 4.4, 2.6 and 2.0 if individuals had not responded to their previous invitation and 1.6, 1.1 and 1.1 if individuals had responded, in the Dutch trial, Piedmont and Reggio Emilia, respectively. Using the measure 'consistency', the estimated detection rate of AN in the fourth screening round for inconsistent individuals were 2.3,1.6 and 1.4 in the Dutch trail, Piedmont and Reggio Emilia, respectively. Based on the measure 'frequency' and 'proportion of invitations covered', the estimated detection rate of AN for inconsistent individuals varied between 1.8 and 2.9 in the Dutch trial, between 1.4 and 2.0 in Piedmont and between 1.3 and 1.4 in Reggio Emilia. Using the measure 'frequency + adherence previous invitation', the estimated detection rate of AN in the fourth screening rounds varied between 18 and 4.5 in the Dutch trial, between 1.3 and 2.0 in Piedmont and between 1.3 and 1.5 in Reggio Emilia. Similar patterns were observed for participation and positivity rate in the fourth screening round. For all three screening programs, the lowest deviance for the estimated detection rate of AN in the fourth screening round was found when using 'frequency + adherence previous invitation' (Table 3). The total deviance for all three screening outcomes was again the lowest for 'frequency + adherence previous invitation'.

3.3. Validation

Our results were robust to the number of screening rounds; the deviance was still the lowest for the 'frequency + adherence previous invitation' measure and the highest for 'adherence previous invitation' (Supplementary Fig. S2). There were small difference in performance in the other simplified measures compared to using four screening rounds. (Supplementary Table S1).

4. Discussion

This study evaluated the predictive value of different simplified measures for longitudinal adherence for relevant screening outcomes in subsequent CRC screening rounds. Our results show that 'frequency + adherence previous invitation' is the best simplified measure of individuals' prior screening adherence to predict the participation, FIT-positivity and detection of AN in the subsequent screening round. This measure could be used to prioritize invitations and/or access to colonoscopy when endoscopy capacity is limited. Also, using these results, longitudinal adherence patterns could be used in risk communication in CRC screening programs, emphasizing the importance of (repeated) participation in CRC screening in individuals that missed prior screening rounds and mentioning the higher yield of screening their case.

Our findings suggest that both recent adherence 'adherence previous invitation' and adherence to prior screening 'frequency' are determinants of participation, positivity and AN detection in the subsequent screening round. This has previously been found in the Dutch population-based FIT screening program; participation in the second round for previously non-attenders was 21.0% compared to 93.4% for previously attenders.(Kooyker et al., 2020) FIT positivity and AN detection in the second round was almost doubled amongst previously non-attenders compared to attenders. This supports the fact that repeated screening is essential in FIT-based CRC screening programs.

Table 2
Participation rate, positivity rate and detection rate of AN for CRC screening observed in the Dutch trial and two regions in Italy (Piedmont and Reggio Emilia) per possible permutation category based on full information of prior participation.

Participation in round 1, 2, 3*	Dutch trial			Piedmont			Reggio Emilia		
	Participation rate	Positivity rate	Detection rate of AN**	Participation rate	Positivity rate	Detection rate of AN**	Participation rate	Positivity rate	Detection rate of AN**
000	14.0%	13.6%	5.1	7.9%	10.3%	3.4	7.7%	7.7%	3.0
100	36.2%	14.8%	4.6	25.0%	8.5%	1.5	26.0%	5.4%	1.9
010	51.1%	12.0%	4.3	38.6%	8.6%	2.4	37.6%	4.4%	0.9
001	73.3%	8.4%	2.3	61.1%	7.7%	2.0	60.3%	5.0%	1.5
110	62.1%	7.1%	2.1	49.1%	7.3%	1.3	56.3%	4.8%	1.5
101	77.2%	7.2%	1.6	68.4%	6.4%	1.7	73.6%	6.0%	1.0
011	87.5%	7.6%	1.9	85.2%	5.7%	1.4	84.5%	4.3%	1.4
111	95.2%	6.3%	1.5	88.9%	4.9%	1.0	94.9%	3.9%	1.0

Abbreviations: AN, advanced neoplasia.
* 0's and 1's designate participation in prior rounds. E.g. 0, 0, 0 = no participation in any of the prior rounds. 1, 1, 0 = participation in rounds 1 and 2, but no participation in round 3.
** Rate per 1,000 individuals

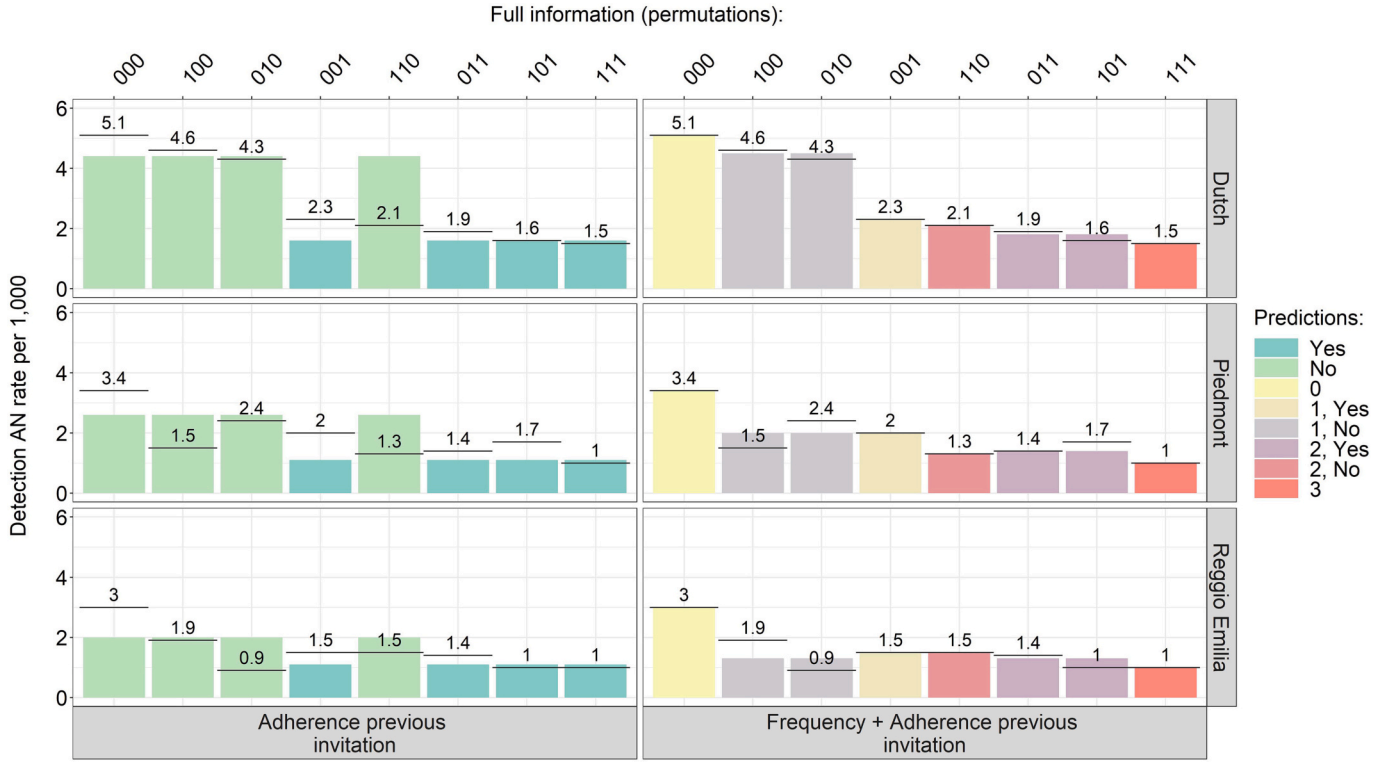

Fig. 1. Estimates for the detection rate of AN in fourth round in the Dutch population-based CRC screening trial and two regions in the Italian CRC screening program (Piedmont and Reggio Emilia) for two simplified measures of longitudinal adherence (the worst and best performing longitudinal adherence measure).
The left panel presents outcomes for the simplified adherence measure "Adherence previous invitation", while the right presents "Frequency + Adherence previous invitation". Each row of panels presents the results for a different screening program: top – Dutch pilot programs; middle – Piedmont; bottom – Reggio Emilia. Each bar represents a different adherence pattern in the three previous screening rounds (see bellows for meaning of the different labels). The height of the bars represents the estimated detection of AN according to the simplified measures, with the colors of the bar representing the simplified category in which the individuals fall. The horizontal black lines with numerical values represent the observed detection of AN per prior adherence pattern. The closer the bars are to the lines, the better is the simplified measure in predicting observed detection of AN.
Abbreviations: AN, advanced neoplasia; CRC, colorectal cancer. Note that 0's and 1's designate participation in prior rounds. E.g. 000 = no participation in any of the prior rounds. 110 = participation in rounds 1 and 2, but not in round 3. The solid black line including the label represents the observed value for the specific screening outcome according to full information of prior participation.

Table 3
Chi-squared deviance for all simplified longitudinal adherence measures in CRC screening in the Dutch trial and in two regions in Italy (Piedmont and Reggio Emilia) considering four screening rounds compared to the observed outcomes with full information of adherence (permutations).

	Adherence previous invitation	Consistency	Frequency	Frequency + adherence previous invitation	Proportion invitations covered
Dutch					
Participation	19,878	8123	2858	708	2858
FIT positives	1413	674	233	60	233
Detected AN	378	182	62	16	62
Total	21,669	8978	3153	785	3153
Piedmont					
Participation	134,815	68,565	23,865	7258	23,865
FIT positives	7712	4574	1569	443	1569
Detected AN	1767	1087	378	107	378
Total	144,294	74,226	25,811	7808	25,811
Reggio Emilia					
Participation	128,616	39,265	13,079	3658	13,079
FIT positives	5287	1887	621	163	621
Detected AN	1466	535	181	52	181
Total	135,370	41,686	13,882	3873	13,882

Abbreviation: CRC, colorectal cancer; FIT, fecal immunochemical test; AN, advanced neoplasia.

Considering these measures separately does not result in appropriate predictions for participation in the fourth screening round as well as FIT positivity and AN detection. The better performance of 'frequency + adherence previous invitation' is at the costs of relatively more information to predict participation, positivity and AN detection compared to the other simplified measures.

Previous research about comparing different longitudinal adherence measures using real-time data is lacking. The commonly-known simplified measures are often used for describing the yield of screening or program adherence to evaluate efficacy.(Doria-Rose et al., 2021) Most earlier studies compute adherence in a single-round which is easy to compute and interpret, but this measure does not take

inconsistent attenders into account. Next, a measure 'program adherence' comparable to 'adherence previous invitation' is being used in multiple studies, followed by 'frequency' and 'consistency'. Our recommendation for use of 'frequency + adherence previous invitation' is in line with the high number of studies using this measure.(Doria-Rose et al., 2021) As in this study, different jurisdictions often adopt different screening protocols, accounting for local organizational constraints, availability of resources and preferences of the target population. The Dutch population-based trial and the Italian programs adopted a different positivity cut-off and targeted different age ranges. Our study shows, however, that differences in program strategies using the same screening interval do not result in a different best predictive measure. Even if the absolute results for each outcome were different, the same simplified measure of longitudinal adherence was able to predict the participation rate, positivity rate and detection rate of AN in the next screening round. Systematic differences in the AN detection rate can be explained by the different positivity cut-off. As FIT-based screening programs often have the same (two-year) screening interval and similar target age ranges, also longitudinal adherence can be compared across programs using this simplified measure.

To actually compare longitudinal adherence patterns across screening programs adopting different strategies such as screening interval, screening age ranges, primary screen test and positivity cut-off of the test if applicable, these measures are not suitable, since they do not take those characteristics of the program into account. With measures like 'Proportion time covered', in which time covered by the program by attending screening and its follow-up procedures is divided by the potential time covered of the program, usually the length of screening interval, program adherence can be compared.(Murphy et al., 2018).

Three limitations are noteworthy. First, the number of advanced neoplasia and, especially, cancers is quite small in the data from the Dutch population-based screening trial. However, in the Italian data, the numbers are much higher and did not result in a different preferred simplified measure. Second, only four screening rounds were included in the main analyses. Sensitivity analysis showed, however, that for five screening rounds in two regions in the Italian program, the best simplified measure was still 'frequency + adherence previous invitation'. Last, our analysis focused on closed cohort (i.e. individuals were eligible and invited over four screening rounds) and therefore 'frequency' and 'proportion of invitations covered' show equal results in screening outcomes and predictive performance. However, when adopting an open cohort approach as well as analyzing patterns of adherence within ongoing screening programs, the number of received invitations might vary by individual and therefore the best simplified measure could be different.

A simplified longitudinal measure can be used in cost-effectiveness modelling to improve their relevance/applicability to real-world setting, using estimates of inconsistent attenders or non-attenders and avoiding unrealistic assumptions of 100% adherence. Additional to the use in modelling, it important to identify patterns of longitudinal adherence to emphasize to individuals the importance of CRC screening based on their adherence pattern: individuals with less recent and lower frequency have higher risk of AN and therefore their risk could be communicated more extensively compared to recent and more frequent participants.

5. Conclusion

Based on data from a Dutch population-based CRC screening trial and from the Italian national CRC screening program in two regions, this study shows 'frequency + adherence previous invitation' calculated based on screening history over the previous screening rounds, is the best longitudinal adherence measure to predict relevant screening outcomes such as participation, screen test positivity and detection of AN in the next screening round. Follow-up studies should confirm our findings also when using an open cohort approach.

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CRediT authorship contribution statement

L. de Jonge: Conceptualization, Methodology, Software, Writing – original draft. **Emilia Riggi:** Conceptualization, Methodology, Software, Writing – review & editing. **Luuk A. van Duuren:** Writing – review & editing. **Esther Toes-Zoutendijk:** Writing – review & editing. **Cinzia Campari:** Writing – review & editing. **Romano Sassatelli:** Writing – review & editing. **Arrigo Arrigoni:** Writing – review & editing. **Lorenzo Orione:** Writing – review & editing. **Iris Lansdorp-Vogelaar:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Carlo Senore:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interests.

Data availability

The data that support the findings of this study are available on request.

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Appendix A. Supplementary data

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