



Perceived influences on smoking behaviour and perceptions of dentist-delivered smoking cessation advice: A qualitative interview study

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Abstract

Objectives: Many factors lead to the commencement and maintenance of smoking, and better understanding of these is relevant in the management of oral health, particularly as smoking cessation advice (SCA) from the dental team is a key component of patient care. Whereas most previous research has focused on dental professionals' perceptions of providing SCA, and identified facilitators and barriers to its provision, there has been more limited research focusing on patients' perceptions of receiving SCA in the dental context. Accordingly, this study aimed to explore the views of smokers with periodontitis receiving dentist-delivered SCA.

Methods: One-to-one, semi-structured interviews were conducted with a purposive sample of 28 adults who smoked tobacco and had recently received SCA during dentist-delivered periodontal therapy. Participants were sampled to reflect a range of ages and smoking behaviours. The interview schedule was based on the Theoretical Domains Framework (TDF) to explore perceived influences on smoking behaviour. Interviews also elicited participants' views on dentist-delivered SCA. Interviews were audio-recorded, transcribed verbatim and analysed thematically, drawing on the TDF.

Results: A broad range of perceived influences on smoking behaviour emerged from the data. Influences were allocated into seven prominent TDF domains: (i) social influences (family and friends, social pressures); (ii) social/professional role and identity (secret smoking); (iii) knowledge (experiences/perceptions of smoking cessation medications); (iv) environmental context and resources (social, home and workplace environment, cost of smoking, resentment towards authority); (v) emotions (stress management, pleasure of smoking and fear of quitting); (vi) nature of the behaviour (habitual nature, link to other behaviours, smell); and (vii) beliefs about consequences (health). With regard to views on dentist-delivered SCA, five main themes emerged: (i) opportunistic nature; (ii) personal impact and tangible prompts; (iii) positive context of cessation attempt; (iv) lack of previous support; and (v) differences between dentist-delivered SCA and other setting SCA.

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Conclusions: Smokers with periodontitis consider that a wide range of factors influence their smoking behaviour. Dentist-delivered SCA was supported and positively received. Important aspects included the opportunistic nature, personal impact, use of tangible prompts and positive context (of the quit attempt). Future research should focus on optimizing dentist-led smoking cessation intervention based on the themes identified.

KEYWORDS

interview, oral health, smoking, smoking cessation, tobacco

1 | INTRODUCTION

The provision of smoking cessation advice (SCA) is an important aspect of patient care. Dental professionals in the UK are advised to provide SCA to all their patients who smoke.^{1,2} A Cochrane systematic review and meta-analysis identified a number of studies exploring SCA delivered in the dental setting and concluded that it can be an effective intervention.³ Smoking cessation is a particularly important aspect of periodontitis management, with tobacco smoking being a major risk factor for disease development, progression and poor treatment outcomes.

A number of cross-sectional surveys have investigated patients' perceptions of SCA delivered by dental professionals.⁴⁻⁷ These surveys generally report a positive attitude to dentist-delivered SCA. Earlier studies reported lower rates of SCA acceptance in the region of 60%.^{4,5} More recent surveys have found 'very positive' attitudes towards dentist-delivered SCA with percentages over 80% reported for dental patient populations in Ireland and India.^{6,7} These cross-sectional surveys are limited by their design in providing any detail or depth of understanding regarding patients' perceptions of SCA. A reasonable body of qualitative evidence exists for dental professionals' perceptions of, and barriers to, providing SCA in the dental setting.⁸ However, to our knowledge, there are no published qualitative studies investigating patients' perceptions of dentist-delivered SCA. Given that qualitative research methods have the power to explore in detail the factors that influence human behaviour, we consider it important to study patients' perceptions, given that they are the recipients of dentist-delivered SCA, and possibly perceive its benefits and limitations differently from the dental team.

Previous research has investigated the psychological, pharmacological and social factors leading to uptake and maintenance of smoking in general populations.⁹⁻¹² However, this has not previously been explored in patients with periodontitis who may have distinctive circumstances and perceptions about smoking. For example, these individuals have often been smoking for many years without being aware of any oral problems, particularly during the early stages of periodontitis. Once diagnosed, and at later stages of the disease process, however, there can be many potentially powerful prompts (eg tooth loss) than can influence smoking cessation attempts. There is currently a lack of theory-based smoking cessation interventions for this group.

The Theoretical Domains Framework (TDF) provides a useful structure for semi-structured interviews exploring behaviour and behaviour change.^{13,14} Developing interview schedules in line with the TDF ensures all potential theory-based determinants of behaviour, and behaviour change can be investigated. The TDF was developed by expert consensus synthesizing 128 theoretical constructs from 40 theories of behaviour into 12 domains (Table S1). The TDF provides a framework for ascertaining the key factors that influence particular behaviours.

The aim of this study was to explore the perceptions of patients with periodontitis about (i) the factors that influence their smoking behaviour, and (ii) dentist-delivered SCA, using theory-based, semi-structured interviews in order to inform future intervention development and optimization.

2 | METHOD

2.1 | Participants

A purposive sample of 28 adults was recruited from a pilot randomized controlled trial (RCT).¹⁵ We anticipated requiring at least 26 participants (13 per trial arm) based on standard recommendations for qualitative interviews.¹⁶ The pilot RCT provided periodontal therapy to 80 adult smokers with periodontitis. All participants were provided with SCA (usual care) with those in the intervention group also receiving the offer of an e-cigarette starter kit. The study design is reported elsewhere in detail.¹⁵ The trial was prospectively registered (<http://www.isrctn.com/ISRCTN17731903>). Potential participants were approached face-to-face at their baseline study visit. All those who were approached to participate in the ages, gender balance, smoking frequency (number of cigarettes/day), nicotine dependence (Fagerstrom's test of nicotine dependence, FTND¹⁷), expired air carbon monoxide (eCO) measurements and RCT group allocation (control/intervention).

2.2 | Interview topic guide development

An interview topic guide was developed by the research team and based upon the 12 domains in the TDF (Appendix A).^{13,14} We

ensured that smoking was explicitly defined at the start of each interview, differentiating it from e-cigarette use or other tobacco product use. Participants were initially asked to confirm the details of their current and previous smoking behaviour, including previous quit attempts. Open-ended questions were asked in relation to each of the 12 theoretical domains in order to elicit responses about a diverse range of factors that may influence smoking behaviour. Questions were also asked about the received SCA. During a TDF training workshop, delivered by experienced researchers in this field, the interview topic guide was piloted with workshop participants and refined. Further piloting was conducted within the research team.

2.3 | Interview procedure

One-to-one, semi-structured interviews were conducted in person, using the prespecified interview topic guide, within a research dental surgery at the Newcastle Dental Clinical Research Facility (Newcastle upon Tyne Hospitals NHS Foundation Trust, UK). An initial interview was conducted shortly after the SCA intervention (usually at visit 3 of the pilot RCT) with a follow-up interview approximately 6 months later (usually at visit 6 of the pilot RCT). The interview topic guide is provided in Appendix A. Appendix B provides further details of the interview procedure and a reflexivity (positionality) statement. The study was approved by an NHS Research Ethics Committee (REC reference: 16/NE/0219). All participants provided informed written consent for participation in the pilot RCT which included the possibility of being invited for interview. A £10 gift voucher was provided after completing each interview. This study adhered to the consolidated criteria for reporting qualitative research (COREQ) and a completed COREQ checklist is available (see Appendix C).¹⁸

2.4 | Analysis

Interviews were audio-recorded, anonymized and transcribed verbatim by a professional transcriber. Field notes were taken as required during the interviews or if participants offered further insight during subsequent dental visits which were not audio-transcribed. The TDF provided the structure for the interview topic guide. The domains were not used as an explicit framework for the analysis, as in some studies.^{19,20} For the data on the influences on smoking behaviour, interview transcripts were analysed thematically by the research dentist (RH) using the TDF domains as an initial framework but with expansion possible after an initial review of transcript content. For the dentist-delivered SCA data, an unconstrained thematic analysis was conducted. Coding was completed using NVivo software (QSR International Pty Ltd. version 11, Edition: Pro, 2015). The dependability and confirmability of the coding and interpretation were checked by a second experienced researcher (SM) during several research meetings, but formal second coding was not completed. These meetings resulted in modifications to the interpretation of

the data based on the input of SM. Data saturation was assessed and confirmed using standard recommendations for qualitative interviews (initial analysis sample: 10; stopping criterion: three consecutive interviews without additional material).¹⁶ Interview transcripts were not returned to participants for comment/correction, although the second interview gave an opportunity for participants to reflect on themes identified from the first interview. Table S2 summarizes these study methods according to the stages for conducting TDF-based research as described by Atkins and colleagues.²¹

3 | RESULTS

3.1 | Demographic data

Twenty-eight participants completed baseline interviews, which were conducted shortly after SCA intervention delivery (6–48 days after intervention [mean: 25 days]). Equal numbers of participants were recruited from each RCT group (control/intervention). Six participants were lost to follow-up, and 21 participants completed a follow-up interview. Further demographic characteristics of the sample are displayed in Table S3. Interview participants were aged 25–60 years (mean age: 45 years). Participants were regular smokers, all smoking at least 10 cigarettes per day (median number of cigarettes per day: 15; eCO: 21 ppm), with a moderate level of nicotine dependence (mean FTND: 5). The interview participants represented a wide range of employment statuses with similar numbers in professional ($n = 9$), intermediate ($n = 9$) and routine/manual ($n = 6$) categories. The baseline interviews lasted between 10 and 52 minutes (mean length: 25 minutes).

3.2 | Influences on smoking behaviour

Smokers with periodontitis, attending the dentist for a course of periodontal therapy, had a broad and complex range of influences affecting their smoking behaviour and views about quit attempts.

For influences on smoking behaviour, interview data were allocated to all 12 TDF domains, although seven of the domains were more prominent: social influences, social/professional role and identity, knowledge, environmental context and resources, emotions, nature of the behaviour and beliefs about the consequences. These themes have largely been identified in previous research and are presented in detail with illustrative quotes in Appendix D. In summary, social influences had an important role at a personal level with family and friends providing social support and having a positive influence on quit attempts. Younger family members often provided most support. Friends who were smokers could have a negative influence on quit attempts. Social influences were also noted at a wider level with participants experiencing social pressure against smoking, often feeling that by being smokers they were part of a minority. Participants were aware of injunctive norms (smoking was not welcome or socially acceptable), and this sometimes led

to attempts at hiding their smoking behaviour ('secret smokers'). Conversely, smoking sometimes had important roles in group identity and influenced motivation to quit. Most of the participants had made several previous quit attempts with extensive use of smoking cessation medications and/or services. Perceptions towards stop smoking medications were largely negative, often citing medication side effects such as mood changes and vivid dreams.

A wide range of environmental factors influenced participants' smoking behaviour. The influence of the workplace was particularly strong and often perceived to be a negative influence on quitting attempts or success. The cost of smoking was sometimes a major consideration for participants with spending on tobacco using up a significant proportion of their income. On the other hand, many participants felt unaffected by this partly due to having sufficient income or (more commonly) access to cheap tobacco (usually illicit tobacco products or purchased while abroad). Emotional influences were impactful on smoking behaviour. Increased stress led to more smoking and was a barrier to successful quit attempts. Life events such as relationship issues, moving house or bereavement were cited as having major influences on smoking behaviour and reasons for previous relapse. The pleasure of smoking was noted by some participants, while others articulated a 'fear' of quitting. Participants were aware of the addictive and habitual nature of smoking, often linking it to other behaviours and habits such as drinking coffee or alcohol. They were aware of the health consequences of smoking, although a small number felt they might be immune to the adverse health effects of smoking, or did not care.

3.3 | Dentist-delivered SCA themes

When considering the dentist-delivered SCA, we conducted an unconstrained thematic analysis (ie not mapped to the TDF) and five main themes emerged: (i) opportunistic nature; (ii) personal impact and tangible prompts; (iii) positive context of quit attempt; (iv) lack of previous support; and (v) differences by comparison with other setting SCA. These five themes are presented in Table 1 along with illustrative participant direct quotations (participant characteristics: gender, age, average number of cigarettes per day). A coding tree is provided in Appendix E.

4 | DISCUSSION

4.1 | Summary of main findings

The interviews explored two broad topics: smoking behaviour and dentist-delivered SCA. In terms of smoking behaviour, this was perceived to be affected by a broad and complex range of influences, as previous studies have also found.⁹⁻¹² Social influences had an important role at both the personal level (family and friends) and a wider level (social pressure). Some participants were strongly affected by social

role and identity and reported being secret smokers. Previous experiences of smoking cessation medications and services were extensive and often negative. Likewise, although a wide range of environmental factors influenced the participants, the workplace was particularly strong in this regard. Several factors were perceived to contribute to a negative influence of the workplace on quitting attempts or success including the following: the availability of tobacco, stress relief and the importance of smoking social interaction (missing out on important business decisions and gossip). Although resources for smoking were sometimes a major consideration (eg high cost), many participants felt unaffected by this partly due to having sufficient income or access to cheap tobacco. Emotional influences were impactful including stress, life events and fear. Participants were mindful of the addictive and habitual nature of smoking as well as the health consequences, although a small number felt they might be immune to the adverse health effects of smoking, or did not care about them.

In terms of dentist-delivered SCA, the opportunistic nature of this intervention was important for several of the participants. Highlighting personal impacts, with tangible prompts, was a powerful motivator for quitting. Framing the advice and subsequent quit attempt in a personal context was seen as useful. Generally, the dentist-delivered SCA was received positively, often being described more favourably than SCA within other settings.

4.2 | Relationship to previous research

With regard to the perceived influences on smoking behaviour, these are largely in keeping with existing research.⁹ Participants had positive perceptions about the dentist-delivered SCA, and, while this is the first qualitative study to examine this issue, the findings are consistent with recent patient surveys.^{6,7} The opportunistic nature of the intervention seemed to carry certain influence, reinforcing existing guidance to healthcare professionals to make every contact count.¹ In the particular context of this study, the participants were also receiving a course of periodontal therapy and several participants were shocked by the severity of their periodontal disease; in some cases, this appeared to have had a synergistic effect with their existing knowledge about smoking harms.

The personal impact of the oral health harms (eg tooth loss, mobility or staining) and early periodontitis treatment results appeared particularly important to participants. NICE guidance on behaviour change²² highlights a number of potentially effective behaviour change techniques based upon the psychological literature including promoting 'personal relevance (emphasizing the personal salience of health behaviours)' and 'positive attitude (promoting positive feelings towards the outcomes of behaviour change)'. This appeared particularly impactful when participants had seen early improvements in oral health from their periodontal therapy.

Elsewhere in medicine, the diagnosis of a significant (smoking-related) disease has been associated with an increased quit rate and an ideal time (a 'teachable moment') for SCA interventions.²³ The findings from the current study suggest that a smoker with periodontitis

TABLE 1 Dentist-delivered SCA themes with illustrative quotations

Theme	Illustrative quotations
<p>Opportunistic nature</p> <p>The opportunistic nature of the dentist-delivered SCA developed as an important theme, with several participants commenting on SCA being unexpected at the dental visit. The opportunistic nature of the SCA was viewed positively by participants, one who described it as an 'olive branch'. The SCA was often linked to the discussions about periodontitis, which also appeared to have a powerful effect on several participants.</p> <p>Several participants reflected on the dentist-delivered SCA being a significant moment in their journey to quitting. Many participants had existing intentions to quit smoking but the dentist-delivered SCA appeared to be a major influencing factor, increasing their motivation to quit.</p>	<p>Just coming in here, like last week, as somebody just offering you an olive branch, that hope, to think, whereas before I was just going on, and I'll get round to it [quitting] one day'. (Female, 58 years, 15 cigs/day)</p> <p>And so it's sort of been like a slap in the face sort of thing, like, 'Oh wow, I didn't realise it was doing that much damage'. (Female, 29 years, 10 cigs/day)</p> <p>I was going to, I had planned on stopping anyway because of, moving house and wanting to stop, but I think sort of the gum disease, sort of, that was the final sort of, made the final decision. (Female, 47 years, 10 cigs/day)</p>
<p>Personal impact and tangible prompts</p> <p>Oral health considerations were commonly referred to as reasons for quitting with participants being particularly concerned about appearance and tooth loss. All the participants in this study had periodontitis and they often referred to the consequences of periodontitis as a motivation for their quit attempt. The personal consequences of adverse effects seemed to be an important consideration. Often the powerful effect of aesthetic consequences was discussed, being perceived as much more impactful than other visual reminders of health harms, such as graphic warnings on cigarette packets. Several of the participants referred to a form of visual prompt that influenced their motivation to quit. For example, the visual appearance of their teeth (eg tooth staining, drifting, tooth loss) or the x-ray appearance were influential aspects of the dentist-delivered SCA.</p>	<p>I know, the problems I've had with my front teeth. And that appears to be linked to smoking, because I started smoking again when issues started to happen and I think my personal appearance and my personal, sort of, feeling towards my teeth are more important and that's why I needed to stop smoking as well... I know, on some packets of cigarettes, there's some photographs and, it still doesn't put you off, but I think when it happens to you, then it's personal (Female, 47 years, 10 cigs/day)</p> <p>...so, when I seen [saw] how bad the back of my teeth are, I don't know how I didn't notice that but, when I did notice that, [laughs] that was a click... (Male, 27 years, 15 cigs/day)</p> <p>I thought me [my] teeth looked disgusting on that X-Ray... 'cos [because] they were coming out of the bone weren't they? (Female, 57 years, 20 cigs/day)</p>
<p>Positive context of quit attempt</p> <p>In this study, the SCA was delivered as part of a course of periodontal therapy. Several of the participants focused their quit attempt on positive aspects associated with reducing the ongoing damage to their periodontal health or with the outcomes of the periodontal therapy eg improved outcomes. Participants sometimes framed their quit attempt in a positive context alongside their periodontal treatment. Likewise, some participants reflected on the positive early outcomes of their periodontal therapy, such as cleaner teeth, as a motivation to quit or remain abstinent from smoking.</p>	<p>I know I'm having treatment but at the end of the treatment as long as I'm not smoking, there is going to be lots of improvement. Rather than carry on smoking and having the treatment it's... it's sort of outweighing itself really, there's not much point. (Female, 45 years, 10 cigs/day)</p> <p>I'm really pleased with, the outcome of that cleaning of my teeth and I really don't want to, spoil it... Yeah, I'm really so pleased, they feel, lovely. Mm-hmm. (Female, 49 years, 20 cigs/day)</p>
<p>Lack of previous support</p> <p>There were some negative perceptions about previous dental care in relation to smoking cessation, particularly around a lack of advice. Sometimes participants felt that previous dentists had not provided sufficient information on smoking and periodontal health. Aspects of blame were sometimes presented, with participants feeling they might have quit smoking by now if they had been told sooner.</p>	<p>...my normal dentist never ever told me it was that [smoking was a risk factor for periodontitis]. It was just some infection I got... I never, I mean, yes, I knew it probably would cause some kind of damage to my gums at some point, but, because I've never been told that, it's never kind of, stuck there. I mean, if I had been told that years ago, when I first started, then probably it would have been a lot easier for me to say, 'Well, I'm going to try'... But like I say, if the dentist had told me it was due to the smoking in the first place... I could have quit the smoking by now. (Male, 60 years, 15 cigs/day)</p>
<p>SCA in other settings</p> <p>The dentist-delivered SCA was received positively by the participants. Many participants felt the dental context of the SCA was different to SCA they had received previously in other settings. Participants often felt the dentist-delivered SCA was more powerful than previous advice they had received because they could physically see the damage caused by smoking, unlike the potential damage on other structures such as lungs. The nature of the professional interaction was also noted with some participants reported that SCA from a general medical doctor felt like a routine 'tick box' exercise. However, when delivered by the dentist, the SCA was perceived to carry more influence for many of the previously mentioned themes: personal impact and tangible prompts, and positive context. However, dentist-delivered SCA did not have a positive effect on everyone with one male participant reporting little impact.</p>	<p>...it's like, it's, coming from a nurse or a doctor who tells you that your lungs is all... you can't see it, so you just think, 'Oh, maybe's[maybe] not me, I'll be alright', but when you can physically see it, and you can see how it's affected me [my] gums... and affected me [my] teeth and the receding of me [my] gums and the bone... I can't see inside me [my] body, but I can see me [my] teeth... I can see the difference that you's [you] are doing, and I can feel the difference that you's [you] are doing (Female, 52 years, 15 cigs/day)</p> <p>...I would say you've [dentist] had much more impact on me, than even, the doctor... I think because, I can't hide me gums from you... you go to the doctor with an illness, whatever it might... and then it's brought up in conversation but it's only for a few minutes. Yes, he's done his job because he's telling you, you know like, you should stop smoking (Female, 58 years, 15 cigs/day)</p> <p>To tell you the truth it didn't make that much effect, 'cos [because] I was already aware that I shouldn't be doing it [smoking] in the first place. (Male, 44 years, 30 cigs/day)</p>

who attends the dentist for a course of periodontal therapy would be receptive to receiving SCA intervention. The concept of a 'teachable moment' is described as 'a particular set of circumstances which leads individuals to alter their health behaviour positively'.²⁴ Lawson and Flocke²⁴ reviewed the literature on teachable moments, finding they were used across a variety of disciplines but were poorly developed both conceptually and operationally. They identified 81 articles, of which only one was in the dental setting²⁵ indicating the potential underutilization of 'teachable moments' to encourage behaviour change within this field and an area for future research. Recent research has identified that short-term health benefits were more influential for behaviour change than long-term benefits.²⁶ This provides further support for the dental setting being a teachable moment where short-term benefits can be seen.

The current study found negative perceptions towards previous dental care in relation to smoking cessation due to a lack of previous advice. This topic is absent from the existing literature, and it would be useful to explore in future research. Future interventions should also consider this in their design.

Finally, with the participants in the current study being long-term smokers, many had received previous SCA from other health-care professionals. Many perceived the dentist-delivered SCA to be different to that from medical doctors. The aspects explored in this section (the opportunistic, personal and positive nature of the SCA) contributed towards the perception that the dentist-delivered SCA (in the particular context of the study) was more meaningful to participants than SCA delivered during a doctor's visit, which might have a perception of 'routine' and a 'tick box' exercise.²⁷

4.3 | Strengths and limitations

This study is the first qualitative research study to investigate patient perceptions of dentist-delivered SCA. The study used the TDF, a comprehensive theoretical framework covering all potential hypotheses for behaviour and behaviour change. The TDF has been used extensively in a wide range of applications.²¹ As this was a qualitative study, the views expressed are unlikely to be representative of all smokers with periodontitis. That said, the characteristics of participants were broadly representative of the general periodontitis population. For example, the age distribution was typical of those presenting with periodontitis and smoking measures indicated a moderate nicotine dependence.

Some limitations of the research are acknowledged. The interviews were conducted within the clinical setting for logistical reasons. The participants were part of a larger clinical study which involved six clinical visits (over approximately 6 months), and in order to minimize participant burden and increase compliance, the interviews were scheduled to run prior to an existing study visit, within the dental surgery. This had the potential to influence the participants' responses; to minimize any effect, the local setting was considered. Participants were seated on a sofa, away from the dental chair, and offered a hot drink in order to help them feel at ease. Interviews were conducted

by the research dentist, which may have influenced the participants' responses. In an attempt to minimize this, the participants were reassured at the start of the interview that there were no right or wrong answers and that their care would not be affected in anyway by their responses. A previous study compared interviews by general medical practitioners and a social scientist and found no differences in how frank the participants were, with similar proportions of critical accounts about health services.²⁸ Nonetheless, the qualitative findings, especially those around comparison to medically delivered SCA, should be interpreted with this consideration in mind.

4.4 | Implications for future research and practice

The findings from this study offer a detailed understanding of the potential influences on smoking behaviour of smokers with periodontitis attending the dentist. There are a broad and complex range of potential influences on smoking behaviour which have largely been explored in previous research. Dentist-delivered SCA was well accepted by participants, and the important aspects of this were the opportunistic nature, personal impact, use of tangible prompts and positive context of the quit attempt. Two more novel themes developed around a lack of previous support (from dentists) and comparisons to SCA delivered in other settings.

Future research should focus on further exploring the themes identified to establish their importance in other populations in the dental setting with a range of disease profiles. Future intervention development should consider the theory-based domains and themes identified as important during their design.

In conclusion, this study found that smokers with periodontitis consider that a wide range of factors influence their smoking behaviour. Dentist-delivered SCA was perceived positively, with important aspects being the opportunistic nature, personal impact, use of tangible prompts and positive context (of the quit attempt). The findings of this study should be used to inform future smoking cessation intervention development and optimization, particularly in the dental setting.

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CONFLICT OF INTEREST

None of the authors declares having a conflict of interest.

AUTHOR CONTRIBUTIONS

RH is the overall lead. All the authors contributed to the design of the study. RH was responsible for the data collection with the support of PMP and SM. All the authors contributed to drafting of the

manuscript and have reviewed the final version before submission. All the authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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