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A qualitative study of physical activity and dietary practices of people accessing Opioid Agonist Treatment in Ireland

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Summary

Background: Active heroin use presents a time of chaotic behaviours, while opioid agonist treatment (OAT) offers an opportunity for people with opiate substance use disorder to improve health and functioning. Lifestyle behaviours of physical activity and healthy dietary practices are increasingly studied for their role in maintaining physical and mental health among people with mental disorders. **Aim:** This research aimed to explore service user experiences of change with respect to physical activity and dietary practices since entering OAT. This research also explored barriers and facilitators to positive lifestyle behaviours among those accessing OAT. **Methods:** Qualitative descriptive interviews were conducted with (n=10) service users using pre-determined themes to explore the aforementioned topic. **Results:** Participants largely viewed lifestyle behaviours as having improved since entering OAT. A number of barriers, such as methadone related symptomology, physical ill-health, and social circumstances were impeding lifestyle behaviours. Physical activity was also impacted by a number of psychological barriers, such as perceived stigma. Facilitators to lifestyle behaviours discussed by participants demonstrated new routines and support structures associated with the OAT service. **Conclusions:** Lifestyle behaviours appear to be positively modified during OAT allied to additional health care supports in place for service users and a potential for improved health and social function. A number of barriers, particularly psychological, remain with respect to behaviour change for this population. This research explores these, with learnings for services to support behaviour change.

Key Words: physical activity; diet; lifestyle; opioid; methadone

1. Introduction

Opioid dependence is a leading substance use disorder among vulnerable sections of the Irish population [3, 7, 9, 16, 20]. Methadone is an opioid agonist treatment (OAT) used in front-line therapy for people with opiate substance use disorder in Ireland. Its use has proliferated community and general practice across the country of Ireland in the past two decades, and is now widely available with up to 10,000 people in receipt of methadone replacement nationally [11].

Among those with substance misuse disorders, there is understandably a strong consideration for physical health interventions [18, 32] that focus on communicable disease [13]. While progress in this

regard has been rapid, an additional burden of morbidity is becoming realised among those recovering from opiate substance use disorders. Emerging evidence shows that people engaged with OAT have a poor life expectancy that is largely attributed to non-communicable diseases, particularly related to poor cardio-metabolic health; a trend that has been widely recognised among other mental health diagnoses populations [21]. Indeed, prospective research in a sample of 114 participants has linked OAT and cardio-metabolic health issues such as weight gain to deleterious lifestyle behaviours such as poor dietary practices [28]. In the past five to ten years, poor physical health has been a consistent focus in the treatment of other non-substance use related mental health di-

agnoses, namely illnesses such as schizophrenia and bipolar disorder [14]. Among the array of therapeutic approaches posed to address this physical health burden, physical activity and addressing poor dietary practices have been identified as viable therapeutic approaches to ameliorate adverse cardio-metabolic profiles [1, 14, 23]. Additionally, both also have a role to play in moderating mental health across different diagnostic groups [15].

Engaging with OAT is often associated with an engagement in health promoting behaviours and a move away from behaviours associated with active heroin use. OAT can also present a time of improved physical health allied to service user behaviour change [19]. However, despite OAT presenting an opportunity to address health holistically, there is a small body of evidence, that shows that people in OAT often adopt or continue to adopt lifestyle behaviours that are health damaging, including consumption of cigarettes and dietary neglect [8, 40]. Longitudinal research investigating the health of people in OAT in Ireland supports the assertion of general health and wellbeing improvement through OAT, characterised by concerted adoption of health promoting behaviours while engaged with OAT [8]. Additionally, qualitative research from the USA shows that people who use drugs can have a heightened awareness towards their health and take an active role in self-care during times of drug using [12]. For example, self-care strategies such as health service utilisation, dietary monitoring and keeping physically active were discussed by people who use drugs as strategies employed offset negative health consequences associated with drug using previously [12].

That said, OAT is not a panacea with respect to health and functioning. Comiskey and colleagues showed that dietary practices among those in OAT in Ireland may worsen following prolonged engagement in OAT of ≥ 3 years [8]. Review research has comprehensively documented a link between patterned opiate use and high sugar content diets [24]. Existing qualitative research has explored the experience of changing dietary patterns among those in OAT living in the UK. A study with a sample of 40 people showed that participants adopt new and more positive eating practices upon commencing residential treatment. However, participants were also prone to a rapid weight gain which generated anxiety among service user with respect to perceived appearance [27]. Aside from this study, there is no research that has qualitatively investigated the barriers and facilitators to eating practices among those in OAT, particularly

in a community treatment context.

Looking to physical activity, people in OAT have a low level of physical activity with respect to meeting activity guidelines for health [6]. Qualitative research has shown that physical activity behaviours may improve, and become more structured upon engagement with treatment services. For instance, research with young male offenders engaged with community re-integration programmes has shown that activity can be viewed as vital mechanism to curb interest in drug using. In this regard, sport and structured exercise is characteristically juxtaposed to lifestyle behaviours associated with illicit substance misuse and associated behaviours. Moreover, activity provides a fundamental, positive replacement with respect to hobbies and interests [35]. Qualitative research among those that use opioids specifically has shown active drug use to be a barrier to physical activity [26]. The work of Neale and colleagues [26], is again reliant on a diverse sample including persons taking prescribed bupenorophine or methadone, persons in residential treatment or community, and so more work is needed to qualify experiences in an Irish community context where methadone is predominantly prescribed. Despite the outlined potential for addressing physical activity and dietary practices of those in OAT, there is an evident sparsity of literature that has qualitatively investigated factors that impede and facilitate physical activity among those that use opiates or avail of OAT [17].

Aim: This research aimed to examine the perspectives of service users with respect to changes in lifestyle behaviours specifically physical activity and dietary practices of people accessing OAT. This research also used qualitative interviews to explore barriers and facilitators to physical activity and healthy dietary practices among a sample of service users in community-based OAT with a view to better understanding factors that influence healthy lifestyle behaviours to enhance future care.

2. Methods

2.1. Design of the study

Prior to the research commencement, a needs analysis was carried out with the relevant substance use treatment services in the South East of Ireland. This work, in conjunction with consideration of the available literature formed the basis of topics to be explored in the research. We carried out a multi-site study using descriptive qualitative study techniques [30, 31].

2.2. Sample

This research adopted a purposive sampling strategy in two community-based OAT clinics in the South-East of Ireland. All participants were attending community-based OAT for opiate substance use disorder. Non-randomised sampling was used during data collection, whereby a sample of (N=10) persons from the involved clinics agreed to take part in the research. Once ten interviews were carried out, data collection was ceased. There were no specific demographic or clinical inclusion or exclusion criteria set. While participants were not required to have ceased heroin use to take part, participants were excluded if they had entered the programme in the past seven days on the advice of clinic management.

2.3. Setting

Each clinic carries out methadone prescribing and monitoring of health and treatment efficacy on a regular basis. Clinics are staffed by a multidisciplinary health team, including a specialist nurse, counsellor and prescribing physician. Each clinic works in close liaison with local pharmacy to provide OAT in a community-based treatment setting. Within the specific treatment settings, advice on physical activity and dietary practices is delivered in an ad-hoc and unstructured fashion.

2.4. Assessment

Prior to carrying-out interviews, a list of pre-determined themes was generated from the concepts to be studied as derived from research questions that were generated during the needs analysis conducted with substance use treatment services. These pre-determined themes were: (I). Changes in physical activity and dietary practices since commencing OAT. (II). Barriers to physical activity and healthy dietary practices. (III). Facilitators to physical activity and healthy dietary practices. Participants were also to provide information on key demographical and clinical variables. An interview schedule using open ended questions was generated by the research team using the predetermined themes which guided inquiry on the factors that influence lifestyle behaviour adoption for people accessing OAT. This schedule also contained a list of probes for each pre-determined theme.

2.5. Procedure

Participant recruitment was initially prompted using advertisements which were placed in the clinic waiting rooms allowing for a period of participation contemplation. Service users that expressed an interest in taking part were verbally informed of the processes, procedures, participant's rights and issued a copy of written participant information. Interested service users were issued with an appointment time and location to attend interview agreeable by both the participant and researcher. Interviews were not conducted immediately, providing an additional contemplation stage. Data collection began following ethical approval and permission from the relevant substance misuse treatment teams. Interviews lasted between 20-40 minutes. All participants maintained the right to review and change their data up until the final stage of data analysis.

2.6. Data analysis

Participants were assigned a code to which only the first author held the key. Only the first and last author were permitted access to audio files during interviews. The interviews were transcribed verbatim and extra care were taken to anonymise data at this point. Following this, multiple reads of the transcriptions were carried out allowing for content analysis to be carried out. This involved the coding of quotations from the transcripts to the relevant predetermined manifest themes that had been developed in consideration with prior literature [5]. Where multiple relevant issues to a theme discussed showed consistency, a new related theme was generated. Demographic data were also gathered to provide a brief description of participants.

2.7. Ethics

Ethical approval was granted from the Health Service Executive (HSE), South-East Research Ethics and Waterford Institute of Technology. A number of procedures were implemented in order to provide robust safeguards for participants and researchers. For instance, interviews were conducted in HSE substance use treatment buildings where the participants were attending for treatment as usual. Every effort was made to remove any identifying features from audio data. All participants completed an informed consent process in addition to undergoing an informed contemplation period. All participants had an opportunity

Table 1. Participant description

| Participant | Gender | Age category | Months in OAT |
|----------------|--------|--------------|---------------|
| Participant 1 | Female | 30-39 | 4 |
| Participant 2 | Male | 30-39 | 5 |
| Participant 3 | Male | 30-39 | 8 |
| Participant 4 | Female | 20-29 | 4 |
| Participant 5 | Male | 30-39 | 8 |
| Participant 6 | Male | >40 | 60 |
| Participant 7 | Male | 20-29 | 18 |
| Participant 8 | Male | >40 | 4 |
| Participant 9 | Female | 30-39 | 42 |
| Participant 10 | Female | N/A | N/A |

N/A = where a participant did not disclose information

to ask questions on the research. Lastly, participants were also provided information for support services before and after the interviews should distress have occurred from taking part.

3. Results

Nineteen service users agreed to participate in the research, each setting appointments to attend for interview. Nine of the agreed participants failed to attend for interview, and recruitment was ceased following data saturation being reached after (N=10) interviews were completed. The sample was 60% male and all participants were of Irish nationality and attending either of the two community methadone replacement treatment clinics for opiate substance misuse disorder in the South-East of Ireland. A further description of the study participants is shown above in **Table 1**.

3.1. Changes in lifestyle behaviours

Prior to questions on barriers and facilitators to lifestyle behaviours, participants were asked to discuss their perceptions of changes to their lifestyle behavioural practices since entering OAT. This data, in addition to wider interview transcripts were subject to frequency-based quantitative content analysis to examine participants' perceptions of changes to their

physical activity and dietary practices since entering treatment. Content were divided into categories; No change, Improved, Worsened. Content were then analysed by frequency of statements to examine how participants viewed changes to their lifestyle behaviours (**Table 2**).

For the most part, participants appeared to report improved practices of physical activity since entering OAT.

Back before the treatment I was only sitting around. You wouldn't be doing anything at all, you wouldn't be moving, walking around or anything like that. Now that I am in treatment, I am doing more exercise (Participant 5, male).

With respect to dietary practices, it was notable that while participants largely reported improvements in their dietary practices, there remained a widespread perception of poor dietary practices among participants. That said, participants largely discussed this to a contrasting experience of not eating at all during times of heroin use.

Since I got away from the heroin and on to the meth (methadone) I have started eating, but I am not eating much now. But, when I was on the heroin I was eating nothing you know? (Participant 6, male).

3.2. Barriers to lifestyle behaviours

While this research had identified Barriers

Table 2. Changes in lifestyle behaviours since beginning OAT

| | Worsened (number of relevant quotes) | No change (number of relevant quotes) | Improved (number of relevant quotes) |
|-----------------------------|--------------------------------------|---------------------------------------|--------------------------------------|
| Physical activity behaviour | 2 | 4 | 7 |
| Dietary practices | 4 | 7 | 12 |

Table 3. Barriers to lifestyle behaviours among those in OAT

| Barriers to physical activity | Psychological barriers to physical activity | Barriers to healthy dietary practices |
|--|---|---|
| <ul style="list-style-type: none"> Loss of employment and financial autonomy | <ul style="list-style-type: none"> Anxiety and panic attacks during activity | <ul style="list-style-type: none"> Homelessness |
| <ul style="list-style-type: none"> Methadone related symptomology | <ul style="list-style-type: none"> Meta-perceptions of stigma | <ul style="list-style-type: none"> Methadone related symptomology |
| <ul style="list-style-type: none"> Physical ill health; Computer games and television | <ul style="list-style-type: none"> Feeling depressed | <ul style="list-style-type: none"> Sustained chaotic routines from times of drug use |
| <ul style="list-style-type: none"> Concern over weather | <ul style="list-style-type: none"> Low self-confidence | <ul style="list-style-type: none"> Physical ill-health |
| | <ul style="list-style-type: none"> Low motivation | <ul style="list-style-type: none"> Living alone |
| | | <ul style="list-style-type: none"> Stress |
| | | <ul style="list-style-type: none"> Low motivation |

to physical activity as a predetermined theme, the analysis of data revealed that psychological barriers to physical activity was also a standalone dominant theme within the data. Therefore, a third theme on Psychological barriers to physical activity was generated in addition to the two predetermined themes outlined (**Table 3**).

3.2.1. Barriers to physical activity

Looking first to the theme Barriers to physical activity, a considerable number of participants viewed methadone related symptomologies as a barrier to their activity behaviour. For instance, many discussed an experience of excess perspiration which was attributed to taking methadone. Participants discussed how such an experience negatively impacted on their aesthetic appearance, this in-turn made physical activity an undesirable activity as it was believed that activity would further exacerbate perspiration.

Yeh. It is dragging me down. Like when I am walking, I find it very hard; very hard to get to the chemist (pharmacy) without pumping sweat (Participant 7, male).

3.2.2. Psychological barriers to physical activity

As already discussed, the analysis of data exploring barriers to physical activity revealed a plethora of factors that warranted the development of a new standalone-theme called Psychological barriers to physical activity. As an example of this theme, many participants discussed the feelings of embarrassment and shame in frequenting very public places to exercise. Participants expressed feelings of being judged by other people because of their drug using past and because of previous links to criminality and known criminals from times of active drug use. Many participants felt that they would only leave their home

when it was absolutely necessary, such as for treatment related reasons.

Plus being a known addict. Being a known addict around, I don't particularly feel comfortable going out walking (Participant 10, female).

Participants were also explicit about their low level of motivation towards physical activity, which was frequently referred to during interviews. Participants identified that chronic drug use had negatively impacted on their daily routine, this was perceived to have had consequential effects on individuals' motivation for physical activity.

I would rather just sit around doing nothing all day. You know, I have to be kinda pushed if you asked me to do anything. That even comes into my recovery or anything like that; I have to be kinda pushed towards it. I don't really have my own motivation (Participant 2, male).

Participants also discussed a perceived effect of methadone on their mood, and a relationship with erratic and unpredictable changes in mood because of OAT.

The methadone. Emotionally and stuff like that, it just, it affected me, it changed me moods, mood swings and stuff like that (Participant, 4, female).

Anxiety and related panic attacks experienced during bouts of physical activity were also discussed as barrier to being physically active. The perceived reason anxiety related panic attacks occurred during physical activity differed amongst participants that discussed it. One participant attributed her anxiety to her clinical depression and characteristic social anxiety. Another participant attributed his anxiety to his recent incarceration. This participant identified that the physiological response during an anxiety attack further deepened his anxiety in the form of fear of triggering another attack.

3.2.3. Barriers to healthy dietary practices

Methadone related symptomologies, and the perceived impact on the individual was the most frequently quoted barrier to a healthy diet. Many participants viewed their methadone as a suppressant to their appetite.

I think that the methadone just fills me up or something; you know, bloats me out. I just don't be as hungry you know, I wouldn't have an appetite (Participant 2, male).

Some participants identified that their eating practices from times during heroin use, reportedly characterised by infrequent meals, nutritionally poor and convenience orientated food choices had followed them through into their treatment, even in the absence of heroin use. This was phenomena coded as 'Sustained chaotic routines from times of drug use'.

Some participants made reference to a number of psychological barriers that they perceived to inhibit healthy eating. For example, the issue of stress as a consequence of a drug using lifestyle arose in a number of interviews.

Everything that I have been through has brought on a lot of stress and then I comfort eat (Participant 7, male).

3.3. Facilitators to lifestyle behaviours

Participants were asked about factors that facilitate them in engaging in healthy physical activity and dietary practices day to day while maintaining engagement with OAT services (**Table 4**).

3.3.1. Facilitators to physical activity

In discussing facilitators to physical activity, participants reflected on new routines resulting from engagement with OAT which were inadvertently increasing levels of activity. For instance, many participants described the process of having to walk to the pharmacy to receive methadone and in-turn the process of having to walk to attend the clinic as a facilitator

to their physical activity behaviour.

I suppose it is to an extent; it's getting me out of the house because I have to go and get the methadone. I can't just ring someone and go, 'here drop that out'. I have to go and get it. So in a way it is a good thing for getting me out and about if you know what I mean? Because other than that, I would never come out (Participant 1, female).

Other facilitating factors to physical activity discussed by participants include 'Activities provided through out-reach programmes', 'Improved self-confidence', and 'Support from family and peers'. More broadly, facilitators to physical activity that were discussed by participants speak to a renewed motivation to seek health promoting opportunities.

My sister in law...like we, we would go for walks because I wanted to tone up me-self a bit and lose a bit off me stomach and that... (Participant 10, female).

3.3.2. Facilitators to healthy dietary practices

The last theme which explored Facilitators to healthy dietary practices demonstrated that participants associated new improved dietary practices with being on the OAT programme. Participants discussed this theme in the context of a change in the frequency and regularity of meals compared to times of active heroin use. Participants also contemplated the role that treatment staff and substance misuse services may have played in supporting them to eat healthier. One participant recounted how staff input had a resulting effect on her giving up high sugar content foods.

Just sick of being told by the nurse that I am drinking too many fizzy drinks. I just said 'sod it'. I gave up 7up. I didn't realise how much I was drinking. I was drinking four litres a day (Participant 9, female).

Table 4. Facilitators to physical activity and dietary practices

| | |
|--|-------------------------------|
| • Activities provided through out-reach programmes | • New routines since OAT |
| • Support from family/peers | • Support from OAT services |
| • Improved confidence since OAT | • Support from family/peers |
| • New routines since commencing OAT | • Weight control |
| • Dog ownership | • Increased motivation |
| | • Increased finance since OAT |
| | • Physical effects of OAT |

4. Discussion

Regular physical activity and maintaining a consistently healthy dietary practices are fundamentally important interventional pillars for protecting the health of people with a range of mental disorders generally [14]. Physical activity and dietary intervention are also an important therapeutic intervention for improving mental health symptoms across diagnoses groups [15]. While communicable diseases remain a challenge for substance use treatment services, there is evidence to show that people engaged in OAT have comparable cardio metabolic ill-health and consequent mortality as that of other mental disorders [21]. In the context of OAT being a widely adopted treatment modality for those recovering from opiate use disorders [11], there seems a need to explore evidenced approaches to moderating physical health for this population.

Looking first to physical activity and people in OAT, structured exercise may have a role to play in treatment of illicit substance use. For example, small scale trial research has shown that exercise may have a positive effect on opiate related craving [2, 39]. Further, evidence synthesis has shown that structured exercise can yield positive outcomes in relation to abstinence rates, mood regulation and improvements to general health and wellbeing among people with substance misuse disorder generally; however the high quality evidence to support these findings is still wanting [38, 41]. Despite these benefits, cross-sectional evidence from the USA inclusive of over three hundred participants has shown that people in OAT have low levels of physical activity, with less than 40% meeting physical activity guidelines for health [6]. Our research here, similar to other qualitative research [26], has indicated that considerable change occurs in the nature and level of physical activity during different treatment types. Indeed, research among young male offenders shows that exercise may be actively sought out and adopted as a diversional strategy for illicit substance use [35]. Yet, there is a clear dearth of research to examine physical activity behaviour in this population which must be considered going forward. Such findings also indicate that there is scope to address behaviour change in clinical contexts to improve the health of person in OAT using structured clinical assessment and intervention.

Our research is important in adding to the sparse literature of qualitative research exploring the experiences of physical activity among those that use heroin or those that access OAT [17]. Relying largely

on one other study [26], qualitative evidence suggests that active heroin use is associated with high levels of incidental physical activity allied to behaviours associated with maintaining habitual drug use, and little or no structured exercise. Our research qualifies these findings, suggesting that people may engage with more structured opportunities to be physically active upon commencing OAT. Participants in previous research [26], have discussed that physical activity practices can become more regular with participants engaging in more structured exercise habits, and also more household chores whilst engaged with an OAT programme. We speculate that such findings are as a result of structured opportunities for activity and that there is a necessity for substance misuse treatment services to consider policy and resourcing for such therapeutic efforts to appropriately support service users. Again, quantitative research would provide important contextual information to examine this matter in more detail. In our research, participants referenced broad holistic markers of general stability, such as new financial independence, and a new social support network. Previous exercise feasibility research has shown that people with substance misuse disorder may require a high level of professional support to engage with therapeutic exercise [4]. These findings support a need for future quantitative research to examine other factors that are broadly associated with levels of activity and autonomous regulation of activity behaviour. Greater autonomous regulation is associated with higher levels of physical activity in other mental health populations [36, 37]. Similar to the aforementioned work by Neale and colleagues [26], our research showed a number of psychological barriers to physical activity were experienced by those in OAT. For instance, in our research, meta-perceptions of stigma stood between many participants and their ability to engage with activities in their local community. Previous literature in the mental health field has identified that such barriers may be overcome through professionally-led interventions to address physical activity self-efficacy [33].

Active heroin use is a time of infrequent eating and skipping of meals, where people are shown to derive no pleasure from food [25, 27]. While improved dietary practice can be observed among those that engage with OAT, dietary practice remain largely deleterious with frequent consumption of processed foods and high sugar content foods [24]. Sustained engagement with OAT services, does not appear to yield better outcomes with respect to dietary practices among service user in Ireland [8]. Our research largely re-

flects this assertion through consensus among participants that their dietary practices had improved since entering OAT. Our research also illuminated poor dietary practices common among participants. Participants described frequent consumption of high sugar content foods such as soft drinks and confectionary and very little consumption of fruit and vegetables, suggesting a need for more integrated clinical intervention to support service user in addressing dietary behaviour change in the community treatment setting. Previous research has shown that well-resourced residential treatment can positively influence dietary behaviour of those in recovery [27]. Indeed, this research alluded the facilitating effects of OAT service for improving dietary practices.

Limitations

This research focused on lifestyle behaviours of diet and physical activity. Future research in the area of protecting physical health of people with mental disorders must take a broad approach to consider other components of lifestyle psychiatry [14, 15]. For instance, between 73% and 94% of people that access OAT use tobacco products, addressing this would have a considerable impact on the physical health of people in OAT [40]. This research focused on the experiences of service users with respect to their lifestyle behaviours. However, such clinical populations also rely heavily on clinicians and professionals in adopting behaviour change [22, 29]. Additionally, substance use research has previously demonstrated ingrained power and stigma related barriers between service users and clinicians [34]. In this research, this phenomena did not arise during data analysis of interviews, however this may also be due to the absence of structured intervention on lifestyle behaviours from existing clinicians. Therefore, therapeutic relationships with respect to lifestyle behaviours may be informal. More research is required to explore this issue. Such investigations should also consider the perspectives of key OAT clinicians in addressing physical activity and dietary behaviour change in OAT treatment settings to understand the multi-disciplinary perspective.

5. Conclusions

There is now a focus and guidance from the mental health literature on implementing integrated lifestyle interventions as part of routine care [10]. In the context of the morbidity burden among people ac-

cessing OAT [21], there appears rationale for well-developed strategy to bring OAT services in line with international mental health examples to make physical activity and dietary intervention a standard of routine OAT care. This research, combined with the work of Neale and colleagues [25-27], demonstrates the need for more specific understanding of the needs of people in OAT. This research identifies that while lifestyle behaviours may improve through OAT engagement, there is considerable room to support service users further in this regard. This research explores barriers to lifestyle behaviours that are inherent to the experience of OAT service users, showing a multitude of psychological and treatment related barriers being experienced by service user. This research also explored experiences to highlight identified facilitators of lifestyle behaviour that have enabled those in OAT to improve and address their health and wellbeing, in addition to providing guidance for services to improve integrated services with respect to physical activity and dietary intervention.

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E.M., M.C., designed the study and wrote the protocol. E.M., managed the literature searches and analyses. E.M., M.C., undertook the statistical analysis, and all the authors discussed the results. E.M., M.C.V.H., F.S., wrote the first draft of the manuscript. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

Conflict of interest

All authors have no conflict of interest.