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ABSTRACT

Citizen science approaches are widely and successfully used in biological, environmental, and ecological sciences; however, they are rarely applied in other domains, such as translational health research, notably in the field of liver disease and metabolism. We have designed a study that aims to explore the application of the citizen science approach in a translational experimental medicine study on non-alcoholic fatty liver disease (NAFLD) and a 12-week lifestyle and weight loss program. In this methodological paper, we describe the process of involving citizen scientists in the study.

We will recruit a convenience sample of 31 participants (with and without NAFLD) and a half-dozen citizen scientists (members of the public). Citizen scientists will work alongside clinical and non-clinical researchers in a translational experimental medicine study on NAFLD. Citizen scientists will be involved in the co-design and/or review of data collection tools (e.g., semi-structured open-ended questionnaire surveys and semi-structured wellbeing diaries completed by the participants), co-analysis of data on participants’ experiences and motivations, co-drafts of research findings and papers, and suggestions for policy recommendations. Citizen scientists will be trained in the research tasks they will undertake, and will be either co-authors or their names will be mentioned in the acknowledgements in research paper(s) based on the level of research contributions.

Lessons learned from implementing citizen science in this study will help to reveal the advantages, limitations, and implications of involving citizen scientists in the translational medicine research. Knowing citizen scientists’ motivations, expectations, training needs, and overall experience of involvement in this study could provide insights, which could inform the planning and conduct of future translational research studies.

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Involving citizen scientists in translational medicine research is an important step in extending research opportunities for members of the public; however, there may be methodological challenges, which may be identified and resolved by more research studies.

INTRODUCTION

Citizen science refers to a research approach in which citizens (members of the public) collaborate with professional researchers/scientists to contribute significantly to scientific inquiry and science (Socientize Consortium 2013) thereby acting as citizen scientists and applying their skills and knowledge to the research process; thus, research is made with, and by citizens (Irwin 2018).

Citizen science is commonly applied in social sciences, humanities, natural sciences (Tauginienė et al. 2020), conservation, biology, digital technology (Kullenberg and Kasperowski 2016) and public health (Rosas et al. 2022). There is a growing interest in expanding the application of citizen science approaches to other fields (Borda, Gray, and Downie 2019; Follett and Strezov 2015) such as the medical sciences (Petersen et al. 2020), and particularly to translational medicine research, where the application of citizen science is still nascent (Carroll et al. 2021). Differences in the focus of research (e.g., nature versus patients), data collection methods (e.g., observation versus skilled medical procedures), and the ethics beyond the corresponding topics (e.g., preserving patients' confidentiality) may explain such differences (Kullenberg and Kasperowski 2016). However, even when the context might be more complicated, the potential benefits of using citizen science across disciplines by making research more accessible, transparent, and relevant to citizens cannot be overlooked (Heigl et al. 2020; Kaye et al. 2012; Wiggins and Wilbanks 2019).

In health sciences, a number of terminologies have been used to describe the implementation of citizen science such as “self-quantification,” “crowdsourcing,” “participatory health,” “action research,” “patient-led research,” and “public and patient involvement (PPI)” (Borda, Gray, and Downie 2019; Borda, Gray, and Fu 2020; Eitzel et al. 2017; Heigl et al. 2020). For example, PPI is used as a way of involving citizens in research to ensure the resulting outputs (which could be practices, procedures, interventions, technologies, etc.) respond to the needs and preferences of the patients and the public (Carroll et al. 2021). PPI is extensively established in the United Kingdom (UK), where its implementation has become a requirement for obtaining research grants from some organisations (National Institute for Health Research 2020). Despite many advantages and successful outcomes, PPI has been criticized for being time consuming, costly, and tokenistic (Blackburn et al. 2018). In contrast, citizen scientists’ involvement in citizen science studies is active, multistage, and voluntary, except reimbursement of some expenses, and there are opportunities for training, learning, and knowledge production (Haklay et al. 2021). In health research, patients have been involved as citizen scientists (Heyen et al. 2022), but it is not always feasible to involve them as such because of the participants’ privacy, a need for anonymity, and other ethical reasons (Groot and Abma 2022). This may suggest involving members of the public as citizen scientists rather than the research participants providing data and taking part in interventional health research. Through this study, we aim to explore the application of the citizen science approach in translational medicine research. This study is being conducted as a part of a European Union–funded citizen science project called STEP CHANGE, which aims to explore and exploit the potential of citizen science for knowledge and innovation advancement and for science and society alignment, through the development and evaluation of five citizen science initiatives (CSIs) in the fields of health, energy, and environment (https://stepchangeproject.eu/). One of these CSIs is the CSI on non-alcoholic fatty liver disease (NAFLD), and it is conducted in the UK, which is discussed in this paper.

Research in NAFLD is important because it is a metabolic disorder (Zarghamravanbakhsh, Frenkel, and Poretsky 2021) affecting about 25% of the global population (Younossi et al. 2016). The prevalence of NAFLD is about 26% in Europe (Bellentani 2017), and it is increasing in several countries (Wong et al. 2018). NAFLD is characterized by excess triacylglycerol accumulation within hepatocytes (epithelial cells of the liver), which can progress to inflammation (non-alcoholic steatohepatitis), cirrhosis, and liver cancer (Ye et al. 2020). NAFLD increases the risk of liver-related and all-cause mortality (Kumar, Priyadarshi, and Anand 2020). There are no licensed medications for NAFLD, and the management currently revolves around lifestyle and weight loss interventions (Esteban and Dinani 2020).

The aim of the CSI on NAFLD is to explore the application of the citizen science approach in translational experimental medicine in the field of metabolic endocrinology.
METHODS

STUDY DESIGN

This is an exploratory study that applies a citizen science approach in a translational medicine clinical experiment. We consider citizen science the involvement of members of the public (citizens) in the scientific research process in collaboration with professional researchers (Rosas et al. 2022). The objective of the clinical experiment is to develop a better understanding of the diurnal variation (along with circadian rhythm) of liver lipid metabolism in overweight individuals under different conditions, that is, with and without NAFLD, and before and after a lifestyle and weight loss (LWL) program. The protocol for the clinical experiment has already been externally, expert-peer reviewed by the funder, and approved by relevant research ethics committee(s) and regulatory bodies (see the ethics approval statement). In this paper, we describe the methodological process of involving citizen scientists in the study. However, to explain the study context, we also report some details of the clinical part of the study.

The study comprises three components: clinical investigations, the lifestyle and weight-loss program, and the qualitative study.

Clinical investigations

Clinical investigations will be conducted in two phases involving individuals with and without NAFLD (Figure 1). The first (initial) phase will involve clinical investigations in the morning (M1) and evening (E1). All participants (with and without NAFLD) will participate in both initial clinical investigations (M1 and E1). At this stage, the involvement of participants without NAFLD will end, whereas those with NAFLD will join a LWL program. Upon the completion of the LWL program, participants with NAFLD will go through the second (final) phase of clinical investigations, which will be again in the morning (M2) and evening (E2). After the completion of the final clinical investigations (M2 and E2), the participation of participants with NAFLD will finish, and the clinical experiment will end. This is an open-label clinical study, and there will be no randomization, comparison, or a control group.

Lifestyle and weight-loss program

All participants with NAFLD will receive a free commercially available LWL intervention. LWL interventions typically include a combination of online, in-person, and app-based information and guidance on dietary intake and physical activity. Commercially available weight-loss programs have been shown to result in greater weight loss (Hartmann-Boyce et al. 2014) than the similar interventions provided in healthcare settings (Jebb et al. 2011). The LWL program, provided by commercial providers convenient to and preferred by the participants, will last twelve weeks.

Qualitative study

This will involve a study of the motivations, expectations, and experiences of all participants (with and without NAFLD). The study will also involve a broader group of volunteer citizens.

Figure 1 Study design. NAFLD: non-alcoholic fatty liver disease.
NAFLD) in the clinical investigations, and self-reflections of participants (with NAFLD) on their well-being and progress during their participation in the LWL program (Figure 1).

STUDY SETTINGS
Participants, with or without NAFLD, living in the community will attend our hospital for the clinical investigations, whereas the LWL program will be offered in the community only to the participants with NAFLD.

RECRUITMENT OF RESEARCH PARTICIPANTS
We will recruit 31 overweight participants (17 with NAFLD and 14 without NAFLD) using the convenience sampling. We will recruit participants from the Oxford Biobank (https://www.oxfordbiobank.org.uk), which is a database of more than 9,000 volunteers in Oxfordshire, England who have undergone extensive metabolic phenotyping and consented to be re-approached for clinical research. Overweight individuals in the top and bottom 10th percentiles of fasting glucose and insulin will be recalled, enriching for the presence of NAFLD and non-NAFLD respectively, which will then be confirmed using magnetic resonance spectroscopy. The inclusion criteria for participants include men and women who are overweight (BMI 25–50 kg/m²) with and without NAFLD and aged between 18 and 75 years. The presence or absence of NAFLD will be confirmed with transient elastography with controlled attenuation parameter ≥ 306 dB/m and ≤ 215 dB/m, respectively (Tavaglione et al. 2022).

RECRUITMENT OF CITIZEN SCIENTISTS
We will recruit citizen scientists from members of the public aged 18 years and above and from diverse sociodemographic backgrounds. Citizen scientists will work as volunteers in the study. For recruiting citizen scientists, there is no recommended sample size, which depends on the type and context of the research study and the research activities they will undertake. A review of citizen scientists’ involvement in public health research found a wide variation in the number of citizen scientists in a study, from 8 to 5,000 (Rosas et al. 2022). In our study, we will recruit about a half-dozen citizen scientists because this is an exploratory study, and we want to have a parity in the number of citizen scientists and professional researchers/scientists involved in our study (n = 5). We will therefore recruit about six citizen scientists, considering an estimated dropout of 20%. We will recruit citizen scientists using the convenience sampling (Chrisinger et al. 2018) and snowball sampling methods (Eleta et al. 2019; Trejo et al. 2021). We will advertise calls for citizen scientists on websites of the STEP CHANGE project and of the National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre, send targeted emails to individuals who belong to PPI panels and obesity and diabetes patient groups, and use social media platforms (such as Twitter) to find potential candidates.

Citizen scientists will be involved for 24 months; however, they will be able to withdraw their consent and leave the study at any time without giving any reason. As citizen scientists contribute in their spare time and on an unpaid and voluntary basis (Pocock et al. 2017), we will let them decide how much time they want to devote to the study and choose when and which research activities they want to participate in.

ETHICAL ISSUES
Research participants
All participants invited to the study will receive copies of the participant information sheet (PIS) and the informed consent form. The PIS will provide details and the exact nature of the study, what it will involve for the participant, and any risks involved in taking part. The participants will be free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give a reason for withdrawal. The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the investigator(s) prior to joining the study. Each research participant will personally sign and date the informed consent form before joining the study.

Citizen scientists
Each citizen scientist will also get copies of the citizen scientist information sheet and the informed consent form via e-mail. The citizen scientist information sheet will provide information about the research study, the roles and rights of citizen scientists, research tasks potentially undertaken by the citizen scientists, and contact details of the research team. Citizen scientists will be given ample time to read the information sheet and ask questions, if any, of the research team. Although seeking a written informed consent from citizen scientists is not very common practice in European citizen science projects (Tsinaraki and Schade 2016), each citizen scientist will complete an Informed Consent Form and send it by email to a designated member of the research team.

DATA COLLECTION
Data from research participants, with and without NAFLD, will be collected by clinical researchers (JWT and TM) as described below:

(a) Clinical investigations
Clinical data will be collected during the Initial and final clinical investigations appointments in the mornings and evenings using validated scales (e.g., International Physical
Activity Questionnaire (Craig et al. 2003) and Pittsburgh Sleep Quality Index (Buysse et al. 1989), and structured diaries (e.g., about food intake in the previous seven days). We will also collect clinical data using non-invasive procedures (e.g., DXA Scan to measure body fat) and invasive medical procedures (e.g., subcutaneous adipose tissue and skeletal muscle biopsies and blood tests).

(b) Participants’ motivations and expectations
We will collect these data using semi-structured open-ended questionnaires during the initial and final clinical investigations appointments. These questionnaires will be prepared in-house by the research team. Clinical researchers will administer the questionnaires and record the responses of the participants.

(c) Participants’ reflective diaries
Only participants with NAFLD will write, on a weekly basis, their semi-structured diaries reflecting on their own experiences and feelings about their well-being, progress, and adherence to the 12-week LWL program. Participants will be provided a blank diary along with an information sheet with basic instructions. However, participants will decide how detailed they want their entries to be. Participants will be asked to return their diaries on the day of their final clinical investigations. Should they forget to hand back their diaries, they will be provided a pre-paid envelope to return their diaries by post.

DATA ANALYSIS
Clinical data collected during initial morning and evening (E1/M1) clinical investigations will be analysed for: (a) primary endpoint: difference in liver de novo lipogenesis (DNL) between morning and evening investigations, and (b) secondary endpoints: liver and global fatty acid oxidation and mobilization. In addition, the diurnal (morning and evening) patterns will be compared between participants with and without NAFLD.

Clinical data collected in the final morning and evening (E2/M2) clinical investigations will be analysed for: (a) primary outcome: change in the diurnal variation of liver DNL before and after the 12-week lifestyle program, and (b) secondary outcome: liver fat fraction and liver and global fatty acid oxidation and mobilization.

All clinical data will be analysed and interpreted by clinical researchers, apart from clinical data collected on the physical activity, sleep quality index, and structured diaries about food intake in the seven days prior to clinical investigations, which will be de-identified and then shared with citizen scientists for co-analysis. In addition, de-identified qualitative data on participants’ motivations, expectations, experiences, and reflective diaries about the LWL program will also be co-analysed by citizen scientists and non-clinical researchers (SGSS, YBM, and VK) with input from clinical researchers (JWT and TM).

Quantitative data will be analysed mainly by frequencies and descriptive statistics using either Microsoft Excel or SPSS (IBM Corp. Armonk, NY), whereas qualitative data will be analysed by inductive thematic analysis (Braun and Clarke 2006) using either Microsoft Word or NVivo® (QSR International Pty Ltd). Identified themes and subthemes will be compared, discussed, and finalized with consensus in joint meetings involving citizen scientists and scientific researchers. Both citizen scientists and scientific researchers (SGSS, YBM, and VK) will identify representative quotes from de-identified participants’ experiences data, which will be finalised by consensus.

ACTIVITIES UNDERTAKEN BY CITIZEN SCIENTISTS
Literature shows that citizen scientists have been involved in different phases of research projects (Rosas et al. 2022), such as the project design development, data collection and analysis, research publications (Borda, Gray and Fu 2020; Heigl et al. 2020), and communication and dissemination activities (Shirk et al. 2012).

Citizen scientists will be invited to participate in different activities except data collection, which will be done by only clinical researchers for ethical reasons. Citizen scientists will complete three online surveys. First, the expectations and motivations survey will be taken soon after joining the study. It’s goal is to obtain the interests and factors that led citizen scientists become involved in the study, and what they expect to achieve through involvement. Second, the training needs survey will be taken a couple of weeks into the study to identify research training needs of citizen scientists. Third, the experiences survey will be taken a few weeks before the end of the project to learn citizen scientists’ overall experience of involvement in the study.

Citizen scientists will be involved in different research activities: reviewing survey questionnaires and a template for the reflective diaries to be completed by research participants, co-analysing deidentified data collected from research participants, co-synthesising the research findings, and co-drafting and reviewing research paper(s) and a policy brief. Citizen scientists will also attend training on qualitative and quantitative data analysis, and participate in participatory evaluation meetings. They will also be involved in project communication and dissemination activities such as writing their profiles for a “citizen scientist of the month” activity and disseminating their activities and involvement in the project via social media. Citizen scientists’ activities and their timeline are shown in Figure 2.
SYNTHESIS AND DISSEMINATION OF FINDINGS

Joint meetings of citizen scientists and researchers will be held to review and finalize the major themes and synthesise the findings. Citizen scientists will be invited to co-draft research findings and papers, which will be reviewed and revised in joint meetings of citizen scientists and scientific researchers.

Study results will be disseminated via presentations at (inter-)national conferences, research open days, and patient and public engagement events, and through journal articles. Copies of the project final report and publications will be provided to the study participants and to citizen scientists on request.

TRAINING OF CITIZEN SCIENTISTS

Citizen scientists require training to contextualize their participation in the study, and discuss and manage their expectations to avoid any deception in research (Eleta et al. 2019). We will survey citizen scientists’ training needs in selected research skills such as co-design and review of data collection tools (i.e., semi-structured open-ended questionnaire surveys and semi-structured well-being diaries), analysis of de-identified data, and co-drafting of research papers. We will ask citizen scientists how, when, and where they would like to attend the training. We will provide training according to the time and day most suitable to the citizen scientist. If a citizen scientist cannot attend a group training session, one-on-one training will be provided. All training will be delivered online by professional researchers affiliated with the NIHR Oxford Biomedical Research Centre.

RECOGNITION OF AND BENEFITS TO CITIZEN SCIENTISTS

To overcome the invisibility of citizen scientists’ research contributions (Kullenberg and Kasperowski 2016) and for transparent reporting of research, we will encourage all citizen scientists to be involved in the co-analysis of data, co-synthesis of research findings, and co-drafting and critical reviewing of manuscript(s), enabling them to meet authorship criteria (COPE 2019; International Committee of Medical Journal Editors 2023). Citizen scientists who do not qualify as co-authors, such as those who assist in writing, technical or language editing, and proofreading will be recognized either individually or as a group, in the acknowledgements in both research paper(s) and project reports. If a citizen scientist does not wish to be named in a research publication, an aggregate acknowledgement as “citizen scientist(s)” will be added.

Literature shows that citizen scientists benefit from their participation in research projects in a number of other ways (Peter et al. 2021; Walker, Smigaj and Tani 2021). In our study, citizen scientists will be offered several benefits such as authorship of research outputs, research skills training, hands-on research experience, health literacy (i.e., learning about NAFLD and lifestyle and weight loss intervention), social learning and networking with professional researchers and other citizen scientists, recognition as citizen scientist of the month, reimbursement of expenses (travel and caring costs), and expertise as citizen scientist (Figure 3).
RISKS TO CITIZEN SCIENTISTS
Citizen scientists involved in research could face health and safety risks, and find research tasks difficult because they are overburdening and time consuming (Walker et al. 2021), but we do not anticipate any health and safety risks to citizen scientists in our study. The level of citizen scientists’ involvement in research tasks will be adjusted according to their availability, research skills, and interests. In the citizen scientist information sheet, we will explain the role of citizen scientists and the research activities in which they will be involved. We will also explore their expectations and training needs to avoid any ambiguity and deception in research (Eleta et al. 2019).

DATA MANAGEMENT AND SHARING
All data, including consent forms collected from research participants and citizen scientists, will be stored on secured computers and managed by the clinical researchers (JWT and TM). Patient data will be de-identified using unique ID numbers before any analysis is conducted. Participants identifiers will be securely stored on encrypted, password-protected computers accessed by only clinical researchers. The data will be retained for five years for research and publication purposes; thereafter, data will be archived according to the Data Archiving and Open Research Policy of the University of Oxford. After the end of the study, archived de-identified data could be made available to other researchers for secondary analyses under an appropriate data sharing agreement according to the data sharing policy and procedures of the University of Oxford. Copies of the citizen scientist information sheet and surveys on the motivation, training needs, and experiences of citizen scientists will be shared with other researchers on reasonable request by email.

DISCUSSION
Citizen scientists (members of the public) can be co-creators of, contributors to, collaborators in, and even initiators of research projects, working together with scientific researchers (Wiggins and Wilbanks 2019). For ethical reasons and because of patient privacy, as well as to avoid any potential conflicts of interest (Kullenberg and Kasperowski 2016), we will not involve citizen scientists in the data collection, but they will be involved in other major research activities including the review and update of data collection tools (e.g., survey questionnaires), co-analysis of data (including data processing such as coding), and annotation and co-drafting of research papers (Borda, Gray, and Fu 2020). In this way, the citizen scientists will co-create evidence and contribute to scientific enquiry. We will also involve them in communication and dissemination of the research findings (Shirk et al. 2012), identifying the target audience, establishing the right language to use, and selecting the appropriate communication channels (Rüfenacht et al. 2021).

In this way, involving citizen scientists in translational health research could help raise public awareness about long-term medical conditions such as NAFLD in both the general population (Ghevariya et al. 2014) and at-risk populations (e.g., diabetic, obese, or overweight people) (Singh et al. 2020; Wieland et al. 2015), which is important because NAFLD can lead to liver cirrhosis, liver failure, and liver cancer (Ye et al. 2020).

The involvement of citizen scientists in our translational medicine study could also promote the use of the citizen science approach in future translational health research conducted at large translational research organizations and centres such as the NIHR biomedical research centres in England, where other approaches such as PPI are widely used, and a standard for PPI has been developed (National Institute for Health Research 2018). In fact, the implementation of PPI in the UK is a requirement for obtaining research grants from research funding bodies like the NIHR (National Institute for Health Research 2020).

Adopting a citizen science approach in research provides members of the public the opportunity to gain hands-on experience in various research tasks and activities around the research cycle. In this way, engaging citizens/members of the public in science and scientific inquiry may help reduce public scepticism of science (Eleta et al. 2019; Follett and Strezov 2015), and make research more accessible, transparent, and relevant to citizens (Heigl et al. 2020; Kaye et al. 2012; Wiggins and Wilbanks 2019). In addition, involving citizens in research studies can also improve scientific literacy (Borda, Gray and Fu 2020) as
well as health literacy, which has been defined differently (for example, see US Institute of Medicine 2004 and World Health Organization 2015). The concept of health literacy has roots in clinical care and public health and it is evolving (Nutbeam 2008). Earlier studies have reported different benefits of involving citizen scientists in (public) health research, such as promotion of health equity (Rosas et al. 2022) and increased knowledge about the research topic(s) or issue(s) (Den Broeder et al. 2018). We believe that citizen scientists involved in our research study would learn more and develop understanding about the health condition (i.e., NAFLD) as well as the intervention (i.e., the lifestyle and weight loss intervention).

LIMITATIONS AND CHALLENGES
There may be challenges in involving citizen scientists in research (Walker, Smigaj, and Tani 2021). For example, citizen scientists’ involvement in the project over the time can be unpredictable (Eleta et al. 2019), and retaining them during the entire duration of a research study is not guaranteed (Follett and Strezov 2015). To ensure citizen scientists’ sustained involvement in the research study, we will iteratively contact them to get their dynamic consent, which is a consent approach that allows people to decide their ongoing participation (Prictor et al. 2020). The dropout of citizen scientists is another challenge (De Moor, Rijpma, and Prats López 2019), and we will tackle it by recruiting new citizen scientists. Additional challenges are the development of research skills (Follett and Strezov 2015) and the training of citizen scientists (Strobl et al. 2020). To tackle these issues, we will survey citizen scientists’ training needs and provide them training in-house. Another noticeable limitation could be the small number of citizen scientists involved in our study; however, their number is almost equal to the number of scientific researchers, which ensures a parity between the two types of researchers involved in our study.

CONCLUSION
Involving citizen scientists in translational medicine research is an important step towards extending research opportunities for members of the public; however, there are several challenges, such as the acceptance of integrating research methodologies of the two domains, citizen science and translational medicine research, which many proponents and practitioners of either domain may find challenging and unacceptable. Nonetheless, additional research studies may help to avoid the scepticism and to increase the acceptance of citizen science methodologies in translational medicine research.

In addition, knowing citizen scientists’ interests and motivations, research training needs, and overall experience of involvement in biomedical research, such as in this study on NAFLD, would also provide insights that could help in planning and conducting future research with citizen scientists.

ETHICS AND CONSENT
This study has been reviewed and given a favourable opinion by the NHS Research Ethics Committee (IRAS Project ID 291205, REC Ref AM02; 20 December 2021), the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) Approval (No. IRAS Project ID 291205; REC Ref AM02; 8 February 2022) and Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) of the University of Oxford (Ref. No. R84742/RE001, 01 March 2023).

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COMPETING INTERESTS
Syed Ghulam Sarwar Shah, Jeremy W. Tomlinson and Vasiliki Kiparoglou are co-investigators and recipients of the STEP CHANGE Project Grant by the European Union (Horizon 2020 Research and Innovation programme, Grant agreement No. 101006386). Other authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS
VK, JWT, and SGSS led the conception and design of this study. YBM and SGSS drafted the manuscript. JWT, VK, and
TM provided critical input and made important contributions to the manuscript. SGSS revised, updated, and finalised the manuscript. All authors have approved the final version of the manuscript. SGSS and YMB are joint first authors.

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