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# Breaking down silos: the multifaceted nature of obesity and the future of weight management

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The continued global increase in the prevalence of obesity prompted a meeting at the Royal Society of London investigating causal mechanisms of the disease, 'Causes of obesity: theories, conjectures, and evidence' in October 2022. Evidence presented indicates areas of obesity science where there have been advancements, including an increased understanding of biological and physiological processes of weight gain and maintenance, yet it is clear there is still debate on the relative contribution of plausible causes of the modern obesity epidemic. Consensus was reached that obesity is not a reflection of diminished willpower, but rather the confluence of multiple, complex factors. As such, addressing obesity requires multifactorial prevention and treatment strategies. The accumulated evidence suggests that a continued focus primarily on individual-level contributors will be suboptimal in promoting weight management at the population level. Here, we consider individual biological and physiological processes within the broader context of sociodemographic and sociocultural exposures as well as environmental changes to optimize research priorities and public health efforts. This requires a consideration of a systems-level approach that efficiently addresses both systemic and group-specific environmental determinants, including psychosocial factors, that often serve as a barrier to otherwise efficacious prevention and treatment options.

This article is part of a discussion meeting issue 'Causes of obesity: theories, conjectures and evidence (Part I)'.

## 1. Introduction

Obesity is a disease characterized by excess adiposity that impairs cardiometabolic, musculoskeletal and psychosocial health [1]. The global prevalence of obesity has risen substantially over the past several decades, with more than one billion adults, teenagers and children living with obesity [2,3]. The increase in prevalence often prompts the questions: 'what causes obesity?' and 'what has changed during the last several decades?' As noted during the 'Causes of obesity: theories, conjectures, and evidence' 2022 meeting at the Royal Society in London, the causes of this complex, multifactorial disease, and its increasing prevalence, are highly debated and there is little consensus among leading experts. Nevertheless, there was a strong concurrence that overweight and obesity are not the result of a collective lack of willpower. It is also unlikely that

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intrauterine exposures, changes in genetic predisposition, or other factors with extended induction periods contributed to the initial increase in prevalence of obesity [4]. Broadly, factors contributing to the development and maintenance of obesity can be categorized into two domains: individual-level and environmental-level contributors. Historically, including the evidence presented during this meeting, the predominant focus of the scientific community has been to identify individual-level determinants of obesity. Despite scientific consensus that environmental, rather than substantial changes to human genetics and biology, are the likely drivers of the modern obesity epidemic, integrating emerging knowledge of environmental-level contributors into studies of the biology and physiology of weight regulation has been sub-optimal.

## 2. Complex interactions

It is helpful to begin by broadly defining the two levels of causal drivers of obesity. Over 90 potential contributors to excess energy storage have been identified [5]. Individual-level contributors refer to those occurring within a person and range from examples such as genetic and epigenetic variability, metabolic and physiological conditions such as chronic inflammation, disturbances to the gut microbiome, mood disorders and endocrine dysregulation (e.g. thyroid dysfunction, polycystic ovarian syndrome and Cushing's syndrome) [5]. Environmental-level determinants refer to those originating outside the body and range from food insecurity, disproportionate access to and affordability of energy dense foods and the vast food environment (which dates back to the 1970s), the obesogenic built environment, socioeconomic status or weight bias and stigma [4–6]. These factors probably interact, with environmental-level influences having a direct impact on individual-level contributors. Conversely, physiological processes can influence how an individual perceives, interacts with, and responds to environmental drivers.

The effect of environmental context in the presence of individual-level factors on body weight is evident in the degree of variability within a given population as it experiences environmental changes. For example, the current food environment has experienced an increase in the prevalence of energy-dense, ultra-processed foods [4]. While modern food processing techniques promote the safety of food, enhance micronutrient content, allow for cost-effective dietary diversity across seasons and ensure adequate food supply to support populations, evidence implicates ultra-processed foods in unintentional weight gain, most likely through increased energy intake and altered biochemical pathways [7–11]. Further, innate and learned food preferences and satiety signals can impact how an individual interacts with the food environment [12]. Specifically, research highlights the neural basis for sugar and fat preference that can drive consumption, craving, and appetite. Exposure to high fat and sugar diets can influence food reward mediated by central dopamine signalling, and promote overeating and weight gain [13]. Importantly, however, cultural, marketing and other stealth strategies (e.g. word of mouth, texts, advertisements on the Internet) that influence eating behaviour, largely precede the development of these physiological drives via cue-driven cravings and behaviours [14]. Food marketing is associated with food preferences, purchases and eating behaviours among children and adults [15,16]. The above reflect only a few examples of how environmental-level factors interact with individual-level factors to influence the development and maintenance of obesity.

Physiology can drive behaviour; however, it is critical to recognize that the manifestation of that behaviour is limited by an individual's available options—the decisions that people make are based on the choices that they have. The location and density of fast-food restaurants, access to nutritious and affordable foods, the walkability of communities, and the availability of recreational spaces are just some of the environmental factors that can be highly variable within a given neighbourhood, region or country (e.g. in the United States (US) by population density, race, ethnicity or socioeconomic status) [17–20]. Thus, the complex interactions between the population-level environmental determinants and individual-level factors are often exacerbated by disparate exposure to desirable versus undesirable environmental factors.

The insidious influence of these sociocultural environmental-level factors extends beyond constraining behaviour to impacting individual-level physiology. Experiencing lower social status is related to a variety of physiological and behavioural changes including chronic and/or acutely increased cortisol, blood pressure, heart rate, visceral adiposity deposition, cardiovascular disease and shortened life span among various animal models [21–28]. Experimentally mimicking conditions of human food insecurity in an avian model through limited and unpredictable access to food promotes metabolic disturbances and weight gain [29]. These findings parallel emerging observations in humans [30]. For example, individuals randomized to experience a lower social status had an increased energy intake and positive 24 h energy balance, particularly for women [31–33]. Ghrelin may be a physiological mechanism behind this response, as those randomized to a low social status experienced an increase in this gastric hormone [34]. Taken together, despite a shared built environment, subgroups that experience poverty, food insecurity, racism and discrimination or other forms of being subjected to a lower social position may be subjected to a more obesogenic environment through these other factors. This, coupled with the downstream impact on physiology, further supports the role of interaction between sociocultural environmental factors and individual level psychosocial stress and physiology.

Despite evidence for the relevance of environmental-level contributors and their interactions with individual-level factors, the focus of the scientific community has largely been on investigating and intervening on an individual level. Historically, the contributing factors to obesity have been simplified to eating too much, moving too little, and possessing too little willpower [35]. Common misconceptions about obesity being an individual-level responsibility, from aetiology to treatment, are apparent in discourse by both the public and members of the healthcare community, and contributes to weight bias and stigma [35,36]. Thus, we argue the long-standing focus to intervene on the individual only, while keeping the environment constant, not only distracts researchers and public health officials, but perpetuates weight bias and discrimination and their adverse impacts on mental and physical health [37,38].

## 3. Optimizing treatment effectiveness and public health measures necessitates understanding and addressing environmental-level interactions

Basic science has elucidated several notable individual level (genetic and physiological) drivers of energy imbalance. Though these mechanisms provide useful insights into the biology of human metabolism and body weight regulation, this knowledge has yet to directly translate to efficacious obesity preventive measures or treatments. Genetic studies, for example, demonstrate that genetic mutations impacting the leptin–melanocortin system cause severe hyperphagia and obesity in humans, but prevalence of these mutations are exceedingly rare. Though this scientific advancement has not informed broad-reaching obesity treatments, they have resulted in effective treatments for those impacted (e.g. setmelanotide) [39,40]. Leptin replacement therapies are highly effective for weight loss among those rare patients with this monogenic form of obesity and in the treatment of lipodystrophy [41,42]. Rather than generating treatment targets, the over 1500 genetic variants associated with body weight may be useful to determine a risk score to reflect propensities for developing obesity [43]. Similarly, research has uncovered that dysfunction within mitochondria, a cellular organelle which converts nutrients into cellular energy, can cause obesity in animals [44,45]. However, although targeting mitochondrial function shows some potential for body weight management, further research is warranted as drugs uncoupling mitochondrial function have historically been unsuccessful and even dangerous for humans (e.g. 2.4-dinitrophenol) [46,47]. Another example, brown adipose tissue contributes to thermogenesis and energy expenditure and insufficient activation can cause weight gain [48]. Pharmacological activation of brown adipose tissue can increase energy expenditure, but whether this can translate to meaningful weight management effects remains to be determined [49,50]. Finally, despite studies investigating whether alterations in gut microbiome profiles relate to changes in body weight in animal models, targeted remediation therapies in humans have produced lackluster results on body weight [51–55]. Despite representing a vast amount of obesity research, it remains to be seen whether additional research to identify population-wide 'defects' or recently acquired 'errors of metabolism' that promote weight gain will translate into effective and safe targets for weight loss.

Effective obesity treatments available today include evidence-based behavioural interventions, anti-obesity medications and bariatric surgery. Behavioural interventions are the least invasive treatment options and often include the patient engaging with a multidisciplinary team to facilitate sustained changes in diet, physical activity and behavioural counselling [56]. These strategies produce 3–10% weight loss on average [57–60]. Pharmacological and surgical treatments are currently available for those with a body mass index of 30 kg $m^{-2}$ or 27 kg $m^{-2}$ with a qualifying comorbidity [1]. Mechanisms of action for currently Food and Drug Administration (FDA) approved anti-obesity medications vary but primarily serve to reduce energy intake via suppressing appetite and slowing gastric emptying [61]. They have historically produced weight loss on average of 3–10%, however, recently approved semaglutide has produced an average weight loss of 15% in clinical trials [62,63]. Additional medications include tirzepatide and cagrilintide. Tirzepatide has produced substantial weight loss, on average 21% of initial body weight [64,65]. Cagrilintide is an amylin-analogue which can be used alone, or in combination with semaglutide to achieve clinically significant weight loss [66]. Notably, tirzepatide is not currently FDA approved for obesity (but is predicted to be by the end of 2023) and cagrilintide is still under development [64,65]. Though invasive, metabolic and bariatric surgery is currently the most effective treatment for obesity to date. The mechanism of weight loss is procedure-dependent, but generally works by influencing appetite, satiety, and neurohormonal feedback, and results in a loss of 24.2% to 37.1% of total body weight on average [67–70]. Considering the chronic and life-long nature of obesity, multiple treatment options may be used in combination (e.g. surgery with pharmacotherapy) to enhance effectiveness for weight management.

Notably, medical, and surgical obesity treatments, while rooted in basic biology and anatomy, demonstrate effectiveness despite not explicitly targeting a specific obesity-related dysfunction. For instance, the evidence demonstrating hypofunctioning of or hypo-sensitivity to gluagon-like peptide 1 in human diabetes and obesity has been inconsistent, yet, increasing the efficiency of incretins by pharmacologically stimulating these receptors at supraphysiological levels produces weight loss [63,71,72]. Bariatric surgery is effective at reducing excess body weight, yet anomalies in underlying gastrointestinal tract structure and lack of stomach restriction are rarely cited as the root cause of obesity. Thus, while the insights provided by basic science have advanced our understanding of individual level factors that can impact body weight, these insights alone have yet to be sufficient in the development of effective treatments. Conversely, while successful obesity treatments may capitalize on our understanding of basic biology, they do not necessarily explicitly seek to target one, specific hypothesized root cause but rather target multiple biological and physiological processes to ultimately promote negative energy balance.

Despite available individual-level treatments, weight regain is common [73]. Owing to the chronic nature of obesity, a range of treatments may be required intermittently to manage body weight for the duration of an individual's lifetime in a similar way to other chronic conditions such as diabetes and hypertension. Similar to varying degrees of weight regain commonly experienced after bariatric surgery, discontinuing lifestyle modifications and anti-obesity medications results in weight regain owing to a variety of biological, physiological, behavioural and environmental factors [74]. Anti-obesity medications should be taken over the long-term and both surgery and medication should be used in conjunction with continued behaviour change interventions to maximize weight loss and continued health benefits. Finding approaches to maximize and sustain treatment effectiveness is of utmost importance and as illustrated above, the environment can modulate an individual's body weight.

Given the interactions between individual and environmental contributors outlined above, it is reasonable to hypothesize that the effectiveness of clinical interventions in real-world settings is limited by the fact that these interventions solely intervene on individual-level factors. Heterogeneity in weight loss across obesity treatment modalities by race, ethnicity and socioeconomic status have been documented in

behavioural interventions, anti-obesity medications and bariatric surgery. In the US, White patients lose more weight than Black, Hispanic, American Indian and Alaskan Native patients for all treatments, owing largely to variations in economic, political and sociocultural determinants of health, rather than genetics [75–83]. Environmental-level factors directly and indirectly impact dietary and physical activity behaviours, acting below conscious awareness [80]. Recommendations for improving racial, ethnic and socioeconomic equity in weight management outcomes include using implementation science (the scientific field of promoting the uptake of evidence-based interventions) methods to optimize the effectiveness of interventions by ensuring that they are acceptable and feasible (e.g. including culturally relevant foods and examples) for all groups [80,84]. Although implementation science has the ability to tailor interventions so they are acceptable and feasible among populations diverse in race, ethnicity and age, treatment effectiveness will continue to be limited by environmental factors such as access to affordable, nutritious foods, housing and transportation policies, and access to insurance and healthcare [80,85–88]. These studies underscore the aforementioned interactions between environmental and individual level factors, and the need for an increased focus on environmental level factors. Access to clinical treatment is important, but a heightened understanding and recognition of how environmental constraints and factors, including those proposed to have contributed to the onset and/or maintenance of the obesity epidemic, influence individual level factors to maintain the disease is crucial to reducing prevalence and incidence of the disease [4]. To witness an impactful reduction in the incidence of obesity, there is a need for equitable access to both evidence-based treatments (e.g. anti-obesity medications and bariatric surgery) and lifestyle modifications (e.g. dietary, physical activity, sleep and stress management modifications), in the context of environmental changes to support behavioural changes.

Without research and consideration of the environmental determinants of obesity and their interactions, the success of biologically based discoveries and treatments will continue to be inefficient and sub-optimally effective on the population level.

## 4. Moving forward: a 'targeted universalism'-based approach for weight management and health

Though research to understand the unique causal factors of obesity in isolation is a noble and worthy pursuit, a multilevel and synergistic approach to this work will be required to move the needle. Based on the evidence presented at the Royal Society meeting, and as we have discussed, the causes are numerous and include multifactorial interactions between contributors in individual-level and environmental-level domains. The objective of the conference was not to pick the theory 'most likely to succeed', and we put forth for consideration that targeting a single 'main driver' is unlikely to translate into an effective solution for the obesity epidemic. Continuing to silo biological versus environmental causes of obesity has proved to be suboptimal and inefficient.

Global trends in obesity demonstrate substantial between- and within-country heterogeneity; thus, despite exposure to generally similar environments, there are individual-level differences in susceptibility to excess weight gain and obesity. The presence of heterogeneity underscores the potential interplay between individual-level contributors (e.g. genetics, biology and physiology) and the environment. Examples are described above; whereby numerous individual-level traits have been examined for their contribution to explaining between-person differences in total or excess body weight. Fewer studies, however, examine heterogeneity in response to an environmental exposure (i.e. interaction between biology and environment), possibly because largescale observational studies or interventions with repeated measures of the genetic/biological factors, environmental exposure and weight change are sparse. Interactions between the environment and individual-level contributors, such as the influence of various diets on physiology of body weight, are under continuous investigation [11,13,89,90]. However, waiting to understand the precise mechanisms by which dietary profiles increase body weight (e.g. diets high in ultra-processed foods) may not be necessary to inform prudent interventions [9,11,13,89,90]. Investigation of the social and demographic factors explaining between-person differences in body weight and weight gain at a population-level is needed. Beyond dietary composition, psychosocial stress, low socioeconomic status, structural racism leading to health inequities and food insecurity impact biology and in part explain differences in body weight and weight gain [29]. It is not entirely clear why investigations into nonbiological bases for obesity (e.g. the food/built environment, social inequity, etc.) have not enjoyed a larger share of the public and scientific discourse, given the relatively rapid rise in obesity in Western countries, with other countries subsequently taking on similar trajectories [91]. A combination of the cognitive ease of pointing to individual responsibility as a common scapegoat and a collective preoccupation with identifying biological-based mechanisms for modern chronic disease has perhaps contributed to the sidelining of more research on overtly non-metabolic traits (e.g. socioeconomic status, food insecurity, etc.) and latent characteristics may be challenging to objectively measure [92]. Although understanding the biology underlying these processes is important, structural changes to environmental-level contributors are central to dampening the impact of heterogeneity in individual-level response to weight management approaches.

A popular refrain is that 'precision' prevention and treatments may provide solutions for weight management. These approaches use largely individual-level factors ranging from genetics and metabolic state to social traits, to determine the best initial treatment approach. However, as with other available treatments, these techniques also rely heavily on the individual to initiate and sustain effort to be effective. This is not to suggest against personalized approaches indefinitely, but to caution that their success, just like long-term success of all weight management interventions, will continue to be limited by the unchanged environmental-level contributors that continue to promote and maintain elevated individual body weight (e.g. unreliable, unaffordable access to low energy dense foods and additional social determinants of health). There is a concern that if a precision-based approach is ineffective, then 'blame' on the individual's lack of willpower or adherence may be particularly high, which stands in contrast to the consensus that obesity is owing due to an individual-level shortcoming or failure [92]. Trends in 'precision'

approaches to obesity in the absence of addressing the broader environmental contributors may be premature. It is useful to consider that precision nutrition may be most beneficial while also addressing the environmental context, but research for these interactions is currently sparse.

If we consider reducing excess body weight and preventing excessive weight gain to be generalized universal goals for longevity and overall health in a population, then we propose considering an adaptation of 'targeted universalism' by Powell *et al*. [93]. Targeted universalism is an approach towards achieving equity by championing the same benefits and minimum protections for everyone, regardless of group membership, by setting universal goals to be achieved through targeted approaches.

More specifically, in its original form, targeted universalism does not advocate for universal policies to achieve these universal goals, as they can create further inequities for certain groups. However, one modification to this philosophy that may benefit the collective goal of managing body weight is a modification to the (universal) food environment. Adapting 'targeted universalism' may include a universal approach such as changing the food environment to reduce the ubiquity of hyperpalatable, low nutrient dense foods, reformulating certain ultra-processed foods to reduce hyperpalatability, changing portion sizes, limiting the use of added sugars like high fructose corn syrup, and considering how, when, and to whom food marketing is targeted and used [4,94]. Most individuals will benefit from making the easy, or default, choice the healthy option as opposed to the current overwhelming availability of cheap, energy-dense, nutrition-poor foods [95,96]. This fosters individual choice and freedom, but the default is a healthier option for an individual's metabolic health and nutritional status. A universal change to the food environment similar to this suggestion may also be an important measure to support targeted approaches (e.g. anti-obesity medications, bariatric surgery, lifestyle modifications) so that they are not stymied by an environment that undermines sustained adherence [4]. Modifying this aspect of the food environment may be one of the most effective routes for reducing obesity incidence at the population-level.

The differentiation between targeted interventions and precision interventions is their scope. Targeted interventions are applied broadly to groups while precision interventions are intended to work at the individual level. Notably, targeted interventions aimed towards the population goal of weight management could serve as an intermediate step between broad policy and precision interventions. These targeted interventions would be applied based on relevant demographic and *broadly* defined phenotypic needs such as socioeconomic status and presence of overweight or associated comorbidities. Identifying targeted interventions to employ to achieve the universal population-wide goal of facilitating weight management will be supported by advancing our understanding of how environmental-level factors interact with individual-level contributors to support or impede weight management. We can identify, design and implement targeted strategies based upon group-level unique needs and circumstances so that each group can achieve parity with the universal goal. One example of a targeted approach includes promoting access to clinical care among those who qualify. Historically, only a fraction of individuals meeting criteria for pharmacological and surgical obesity treatment have the opportunity to use this treatment. Of those who qualify, only 2% and 1% of patients use anti-obesity medications and bariatric surgery respectively owing, in part, to lack of insurance coverage [97–100]. Further, patients who do take anti-obesity medications may be forced to pay out of pocket as many insurers do not reimburse for obesity treatment. In consideration of newly approved, highly effective obesity drugs including semaglutide, interest in use may increase but access and expense may be a barrier to utilization, particularly for those most at risk of further health inequities (e.g. racial and ethnic minority groups with lower financial resources). Applying a targeted approach to increase access might therefore involve providing price adjustments to these treatments based on demonstrated financial need. A similar process of price adjustments or targeted approaches based on financial needs could be applied for those who qualify for metabolic and bariatric surgery. Wider access and use of medical treatments for obesity warrant an emphasis on healthful dietary and behavioural modifications as these treatments in and of themselves do not promote healthful dietary patterns, sleep regimens, stress management or physical activity levels. For example, treatment approaches that decrease appetite to reduce energy intake have the potential to cause or exacerbate deficiencies of nutrients critical to physical and mental health [101,102]. Thus a targeted approach to support individuals receiving treatment could be expansion of a behaviour change programme focused on nutrition, physical activity, sleep, and stress management in adjunct to medical treatment of obesity. Relatedly, secondary targeted interventions to support nutrition quality in the context of weight management include strategies to increase access to safe and healthy foods. While efforts to move the needle on obesity by increasing fruit and vegetable intake have been less impactful than expected, fruit and vegetable intake is associated with improved diet quality and nutrient intake [103,104]. Strategies to increase access to nutrient dense foods, such as implementing full scale grocery stores rather than corner stores, may support optimal nutritional status in vulnerable communities with lower socioeconomic status. Individuals who positively screen for food insecurity could receive targeted interventions to address this without additional stigma such as reliably scheduled receipt of groceries. Ultimately, targeted medical approaches must be paired with evidenced based behaviour change programmes and concurrent shifts in environmental level factors that facilitate healthful behaviours to both optimize weight loss and overall health and wellness.

The targeted universalism-based approach proposed above lends itself to a layered approach to address obesity. Population-level reductions in excess body weight and prevention of excess gains may be most effectively and efficiently attained by modifying the environment itself. In scaling the targeted approaches to the level of group phenotype/group characteristics, each designed to meet specific needs of the group to achieve the universal goal, both population-level and individual-level interventions are required. In the future, research into basic biology may be able to better identify 'obesity' phenotypes and genetic risk scores may also further inform targeted universalism based approaches, assisting in identifying at-risk groups who may benefit from additional preventive measures and interventions. In conjunction, finely tuned adjustments at the level of the individual may be made with eventual advancements in precision nutrition. There will consistently be the interaction between the individual-level and

environmental-level contributors, so both are needed—not solely individualized targeted nutrition interventions out of context of the environmental setting. This may help provide a synergistic effect between the individual level components while also acknowledging the sociocultural components that contribute to development of obesity.

## 5. Conclusion

In conclusion, while continued investigation of the causes of obesity will provide valuable insights, environmental-level causes are critical components and currently understudied. To address the high prevalence of obesity the following actions are required: (i) enhance access to affordable evidence-based medical interventions (e.g. anti-obesity medications and metabolic and bariatric surgery) and lifestyle modification programmes (e.g. dietary, physical activity, sleep and stress management), and (ii) investigate effective environmental changes (e.g. food environment; socioeconomic support to minimize psychosocial stress) to address determinants of obesity and to support existing treatment modalities. One way to implement these requirements is through a layered, approach adapted from targeted universalism which sets universal goals that benefit the health of all individuals within a population, with tailored approaches to meet the needs of broadly defined subgroups based on, for example, demographics, socioeconomic status and weight status. Research is warranted to further delineate the most impactful environmental drivers amenable to modification. Examples may include changing the physical built environments and reformulating certain ultra-processed foods to reduce hyperpalatability. Targeted approaches could attempt to use current understanding in environment-individual interactions, although more research is needed in this space as well including the adaptations in appetite regulation owing to ultra-processed foods and obesity. Ultimately, these approaches may enhance the effectiveness of current and future therapies, including precision nutrition. Obesity is the result of interactions between individual and environmental-level contributors, and research into these complexities are lagging investments in basic biology. Although knowledge on the individual-level contributors provides helpful insights, to effectively reduce the incidence of obesity, addressing the environmental context is ultimately required. It is difficult to continue to ignore the futility of attempts to reduce the incidence of obesity by intervening on the individual level, then placing patients directly back into the environment that contributed to the development and maintenance of obesity in the first place.

Data accessibility. This article has no additional data.

Authors' contributions. F.A.N.H.: conceptualization, writing—original draft, writing—review and editing; V.L.D.: conceptualization, writing—original draft, writing—review and editing; S.E.D.: conceptualization, writing—original draft, writing—review and editing; S.M.: writing—original draft, writing—review and editing; D.T.: conceptualization, writing—original draft, writing—review and editing; M.I.C.: conceptualization, writing—original draft, writing—review and editing.

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