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Overview

Aims and Scope

Lifestyle Medicine is a peer-reviewed, open access, interdisciplinary journal providing a forum for all those interested in the rapidly growing specialty of lifestyle medicine. The journal considers articles and reviews which focus on the clinical and scientific aspects of lifestyle medicine and its incorporation into clinical practice.

At *Lifestyle Medicine*, we aim to be a truly global forum for academically rigorous research, and we think that the best research should be published and made widely accessible as quickly as possible. We advocate the principles of sound science publishing. We only accept papers where the conclusions are substantiated by the data presented. If the science is reliable and sound, we will publish.

In order for research to advance, negative results, which often make a valuable contribution to the field, should be published. However, articles containing negative or null results are frequently not considered for publication or rejected by journals. We welcome papers of this kind, where appropriate and valid power calculations are included that give confidence that a negative result can be relied upon.

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Keywords

Aerobic exercise, Alcohol consumption, Alcohol excess, Antidepressant medication, Arthritis, Atherosclerosis, Back pain, Balance and gait, Beck Depression Inventory (BDI), Behaviour change, Body mass index, Bradykinesia, Cancer, Cardiometabolic diseases (CMDs), Cardiovascular diseases (CVDs), Cerebrovascular disease, Chronic pain, Chronic disease, Chronic illness, Clinical depression, Coaching, Cognitive Behavioural Therapy, Complications, Consumer culture/materialism, Counselling, Credit card debt, Dance, Data analysis, Debt, Dementia, Diabetes Distress Scale (DDS), Diabetes Family Behaviour Checklist (DFBC), Diabetes Mellitus, Diabetes Self?Care Activity Scale (DSCA), Diabetes-related distress/depression, Diet, Dietary intervention, Drug-free, Dyslipidaemia, Empowerment, Emotional support, Epidemiology, Ethanol, Exercise, Exercise prescription, Feasibility studies, Fibromyalgia, Financial Stability/hardship/debt, Football, Gardening therapy, Goal, Green space, Group clinics, Group consultations, Healthy living, Health coaching, High blood pressure, High intensity exercise, Holistic, Hypercholestrolaemia, Hypertension, Inflamm-ageing, Inflammation, Insomnia, Insulin resistance, Intelligence quotient, Lifestyle choices, Lifestyle factors, Lifestyle interventions, Lifestyle Medicine, Lifestyle practices, Lifestyle Psychiatry, Longevity, Long-term conditions, Low carb diet, Medical Screening, Meta-analysis, Metabolic biomarkers/signatures, metabolic disease, Metabolomics, Metabotype, Mindfulness, Mitochondrial Dysfunction, Moderate exercise, Mood and Wellbeing, Mood state profiles, Motivational interviewing, Motivational counselling, Musculoskeletal medicine, Narcolepsy, National Screening, Neck pain, Neurodegenerative disorder, Neuropathy, Nicotine replacement, Non-communicable diseases (NCDs), Nutrition, Pain, Pain management, Parkinson's Disease, Patient Activation, Patient-centred/centered, Peer support, Periodic health evaluation (PHE), Personalised care, Personal target, Personal goal, Pet ownership, Physical activity, Plant-based diet, Positive thinking, Prescription drugs, Prevention, Primary prevention, Secondary Prevention, Psychology, Psychopharmacology, Psychotherapy, Public health, Quality of Life (QoL), Recovery strategies, Refreshing sleep, Regression analyses, Relationships, Remission, Resistance exercise training (RET), Retinopathy, Reversal, Screening, Secondary prevention, Self-care plans/programmes/management, Self-efficacy, Self-management, Shared medical appointment, Shared decision-making, Sleep cycle, Sleep hygiene, Sleep pattern, Sleep prescription, Social Media / Smartphone Use, Social/ emotional support, Sport, Spouse/family support, Strengthening exercise, Stress, Stress management, Substance abuse, Substance misuse, Swimming, Tai Chi, Target weight, Treat to target, Total Mood Disturbance (TMD), Toxins, Vigorous exercise, Virtual group consultations, Video group clinics, Wellbeing, Wellness, WHO-5 Well-Being Index, Whole food, World Health Organisation, Yoga.

Open Access and Copyright

Lifestyle Medicine maintains the highest standards of peer review while increasing the efficiency of the process. All research articles published in the journal undergo full peer review, and we pursue editorial approaches that may help us avoid bias. We do our utmost to judge research objectively on its own merits and to avoid favouring research, for example, from particular institutions, countries, or regions. Key characteristics of the journal's review process are:

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- Members of the editorial board lend insight, advice and guidance to the Editor-in-Chief generally and assist in decision making on specific submissions.
- The managing editor and editorial assistant provide administrative support to ensure *Lifestyle Medicine* maintains the integrity of peer review and delivers rapid and efficient publication to authors and reviewers.

The journal will be applying to appropriate abstract and indexing services to ensure wide visibility of articles published in *Lifestyle Medicine*.

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COMMENTARY

What the obesity epidemic does not need: A cancel culture

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A paper recently published in *Lifestyle Medicine* highlights the importance of informed and respectful debate as part of the scientific endeavour. Appearing in the first edition of the journal, Jacob et al.[1] examined data from 7403 participants from the 2007 Adult Psychiatric Morbidity Survey (APMS), a nationally representative survey of the English adult population conducted by the National Centre for Social Research and Leicester University.[2] They found that there was a negative association between Verbal IQ, estimated using the National Adult Reading Test (NART), and obesity. During peer review, the manuscript was praised for its clear and robust statistical analyses. However, due to the nature of the topic, editorial review included assessing the manuscript for inappropriate or discriminatory language or conclusions, as well as ensuring both scientific and analytical merit in line with the journal's scope. Perhaps unsurprisingly, the paper still resulted in significant vocal debate on social media (Twitter), including calls for the paper's retraction. As Twitter does not uniformly allow for reasoned discussions, formal letters to the editor were solicited by Wiley to highlight any significant issues and allow for formal response by the original authors. This process is still an important aspect of moving scientific research forward, and as a journal we follow both International Committee of Medical Journal Editors (ICMJE)[3] and the Committee on Publication Ethics (COPE) publishing principles,[4] which include giving a platform for rebuttal to published articles and encouraging logical and reasoned scientific debate. Both the letter to the editor by Redsell et al.[5] and the response by Jacob et al.[6] are included in this issue. While we stand by the publication of the manuscript – as further outlined below – we believe that it is the job of the scientific community at large to iteratively move a field forward based on discussions such as those highlighted here. Therefore, to some extent, each reader can and will make up their own minds based on the evidence, following scientific principles to do so. We hope this commentary assists that process.

1 | SCIENTIFIC OBJECTIVELY

Using weight or normative estimators of body composition, such as the body mass index (BMI), as predictors of individual health or health outcomes is both controversial and highly emotive.[7] This is clear from the tone of both the letter by Redsell et al.[5] and the response by Jacob et al.[6] One thing that we feel is absolutely necessary in order to move discussions in this field forward is the separation of our personal feelings about a topic from the scientific arguments, as much as that is possible. In line with that, both the letter writers and article authors were given opportunities to tone down their language, and both articles have been lightly edited (in language but not content) to more constructively moderate the discourse.

2 | THE COURT OF PUBLIC OPINION

A discrete focus on the scientific arguments and process of a manuscript is important because Redsell and co-authors present unsubstantiated accusations such as that the manuscript is 'ill-advised (at best)', and include veiled threats that 'this paper is also likely to cause harm, which may risk reputational damage'. The latter assertion was largely focused on how the findings may be portrayed by the media. We absolutely agree that accurate reporting of scientific findings in the media – as well as ensuring that research is not discriminatory – is an essential part of science publication and communication. However, the

broader implication in the letter appears to be that research into populations at particular risk of, or potential downstream (health) consequences of, obesity should be avoided because it may be inaccurately portrayed in the media and used to propagate weight stigma. This argument also includes *non-sequiturs* in the assumptions that risk factors for obesity usually regarded as non-modifiable are not of interest for potential targeting of modifiable risk factors, and that patients and the media will necessarily fuel negative stereotypes. Patients, including the patient representative who helped write the editorial in our last issue,[8] are clear that they want to see the evidence for themselves, which the open access model supports. Therefore, it would be a curious approach to sanitise the content due to potential for misinterpretation rather than accept submitted articles based on their scientific quality.

3 | FLAWS… OR NOT

Redsell et al.[5] also suggest that the original study suffered from a number of methodological flaws and breached two ethical principles (beneficence and justice). Though there is some discussion regarding the utility of the National Adult Reading Test in this setting, no clear methodological flaws – either in the analysis or the interpretation – were raised. We agree that the quality of a data used to examine a specific question can almost always be improved. For instance, it must be recognised that societal inequities are significant drivers of both obesity and 'performance' in normative tests such as those for intelligence quotient (IQ)[9] with the history, use, and interpretation of the original IQ tests grounded in both sexism and racism.[10,11] Jacob et al. performed multiple sensitivity analyses to adjust for individual background and environmental factors that might influence the outcome, but the direction and magnitude of the effect remained consistent. Importantly, though the authors could have been more explicit about other unknown confounders, as well as the fact that socioeconomic parameters such as race, income, and education are often proxies for much greater social inequities and a wide range of lived experiences,[12] they performed appropriate adjustments with the available data and were clear about the limitations. This does not preclude the possibility that different results will be seen in the future if datasets containing a broader range of equitable cognitive tests and accurate body composition measurements are collated and analysed. Advances in epidemiology like other branches of science is iterative and while no clinical research study is perfect, constructive criticism is a key driver of improving study design and conduct.

4 | NOT INFERRING CAUSATION

The intended goals of public health epidemiology, and what can and cannot be concluded from a particular dataset or analysis, is a crucial aspect of evidence-based medicine. Redsell et al.[5] do rightly state that the original manuscript only 'explores the association between IQ and obesity, not causation', while also accusing the authors of implying causation. The former is absolutely true, as is the case with any epidemiological study, but Jacob et al[6] clearly do not attempt to assume causality, presenting previous work that could drive causality (if present) in either direction. Multiple factors may explain the results, from unknown confounding by socioeconomic and environmental factors to an inflammatory phenotype associated with visceral adipose tissue that may impact the brain,[9,13] and while these questions remain it is imperative that objective research continue. The way the results are written by Jacob et al. is largely driven by the requirements of multivariate statistical analyses, where a response variable (in this case obesity as a binary outcome) must be chosen, along with associated predictor variables. The outcomes of these models include an odds ratio for obesity, but do not imply that the predictors (e.g., Verbal IQ) are directly causative.

Redsell et al.[5] do also highlight papers that support the potential for better metrics and assessments for use when studying this question in the future, though one might argue that their representation of cited literature differs from that stated in the papers themselves. For instance, citing McGurn et al. as evidence that the performance of the NART was only modest when that paper describes a strong enough correlation to validate the use of the test.[14] As with any standardised test, we agree with Redsell et al.[5] that the variance in NART scores (as well as BMI) due to other factors such as material and social deprivation is both possible and likely, but this is at least partly addressed by the statistical adjustments and does not invalidate the results as presented. We also agree that self-reported BMI does not perfectly reflect clinical measurements,[15] as also acknowledged by Jacob et al.[6] in the original manuscript, although self-report is generally regarded as a valid approach. If anything, self-report is likely to lead to an under-estimate of BMI so is likely to have underestimated the prevalence of obesity in this dataset and as such diluted any associations.

5 | CITATION AND SOCIAL MEDIA

Correct attribution and citation is important, so the letter includes full references inserted at the proofing stage, which clarifies which publications (especially newspapers) may be more likely to misinterpret the science and create headlines, albeit that the references are not recent or relating to policy in the country of publication. We do operate in an international environment, so global awareness is important too, both in not bowing to excessive perceived pressure from the approach of certain UK newspapers nor being influenced by censoring in more totalitarian regimes. There is a balance to strike here: recent events in the Washington Capitol and social media's involvement and subsequent repudiation of longstanding approaches show this is a developing area.

6 | RESPECTING INDIVIDUALS, INFORMING POPULATIONS

We do strongly believe that every person has the right to feel safe, comfortable, and happy in their body, and multiple studies have indeed

shown that damaging weight stigma is incredibly prevalent in the popular media, contributing significantly to society's negative viewpoints around body weight.[16] Work by the "health at every size" (HAES) movement is both important and growing, often highlighting the fact that societal weight stigma and diet culture can significantly negatively impact the health and quality of life of certain targeted individuals,[17–20] as well as the fact that BMI or body composition may not be deterministic with respect to long-term health outcomes.[7,21,22] These are important issues must be addressed head-on, for instance by tackling dangerous aspects of diet culture and media misrepresentation of weight and health, as well as clearly separating out epidemiological work designed to improve risk stratification and policy at the societal level from the nuanced, holistic, and personalised approaches that should be taken to improve an individual's health trajectory with their consent and concordance, which will most often include interventions that are weight neutral. These societal issues should not, however, prevent obesity research at the population and mechanistic levels being performed to identify those at risk, or potential interventions, particularly within systems and institutions. Identifying at-risk populations to help institute systemic change, rather than place health solely as the responsibility of the individual[23,24] is an important goal of research using population datasets such as that presented by Jacob et al.,[1] and these studies are never intended to be used to make statements about individuals. However, there is compelling evidence that obesity is a strong driver of poor health outcomes, more powerful for many than physical inactivity.[25] Depending on the criteria used, 7–50% of those with obesity are metabolically healthy,[26] but even metabolically healthy obesity appears to be associated with an intermediate risk profile for outcomes such as cardiovascular disease.[27] Recent systematic reviews have also suggested that (i) weight loss interventions may improve health-related quality of life, with the effect potentially correlated with magnitude of weight loss,[28] and (ii) that behavioural weight management interventions result in improvements in a number of mental health outcomes, including body image concerns and self-efficacy,[29] without negatively impacting overall mental health. None of this negates an individual's experience of weight and weight stigma, but instead highlights the importance of objective assessment of the evidence at a higher level coupled with individualised patient-centric approaches. Therefore, those who want to help those impacted may be better served by encouraging the use of valid tools for both population and individual risk assessment, as this can inform empowering choices by the individuals, when shared in appropriate ways, which will vary by country, setting and individual.[30]

In summary, with respect to the original manuscript and subsequent communications, we respectfully maintain that the original manuscript meets our criteria for publication. Retraction is not justified on the basis of the arguments presented. However, we welcome rational scientific debate and hope that by publishing both the letter and reply we can encourage a constructive collaborative approach to destigmatising obesity rather than shaming those who do not avoid addressing difficult and complex issues.

CONFLICT OF INTEREST

FB is Editor-in-Chief for the Wiley open access journal *Lifestyle Medicine* and Director of Science and Research for the British Society of Lifestyle Medicine. SK is a bariatric physician, Regional Director for South Wales & on Nutrition Interface Group for the British Society of Lifestyle Medicine. TW is an Associate Editor for the Wiley open access journal *Lifestyle Medicine* and is a Trustee of British Society of Lifestyle Medicine.

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LETTER TO THE EDITOR

Concerns regarding "Association between intelligence quotient and obesity in England" and unjustifiable harm to people in bigger bodies

Dear Dr. Birrell

November 26, 2020

Dr. Fraser Birrell

Editor-in-Chief, *Lifestyle Medicine*

We write to express our concern about a paper you recently published in your newly established journal. The paper examines the association of a non-modifiable measure, IQ, and its relationship to adult body mass index (BMI). We are academics, health professionals, health psychologists and lay experts in weight stigma and discrimination, public health, patient advocacy and risk communication. We believe the contents of this paper are likely to cause unjustifiable harm to people in bigger bodies, some of whom may not be in a position to raise their concerns with the authors or yourselves. We further assert that there are numerous ethical and methodological issues that should be brought to your attention, which limit the applicability of the results.

This paper goes against the stated aims and the scope of your journal. First, your journal states that you "advocate the principles of sound science publishing" and that "if the science is reliable and sound, you will publish." Yet this paper suffers a number of methodological flaws and, in particular, breaches two ethical principles, namely, beneficence and justice that significantly detract from the soundness of the science. As we demonstrate below, on this occasion your journal has not upheld good scientific principles. Second, you state that your journal "examines clinical and scientific aspects of lifestyle medicine and its incorporation into clinical practice." This suggests that you are interested in research that identifies potentially modifiable risk factors that might be addressed in clinical practice in a way that is beneficial to people. IQ is neither a "lifestyle" choice nor a modifiable variable (as noted by the authors themselves). IQ is a highly heritable trait,[1] which can be influenced by environmental factors,[2] most of which are unmodifiable from an individual perspective. We outline our remaining concerns below, along with the scientific evidence that supports them.

1 | HIGH RISK OF HARM

The paper is openly available for anyone to read online, including practitioners, researchers, decision-makers, the general public, and media outlets. Indeed, such articles are often misinterpreted in the media, adding to inaccurate portrayals, and the stigmatisation and discrimination of people with bigger bodies.[3] The media frequently incorrectly attributes personal responsibility[4] to people with bigger bodies and we believe that this article feeds into an unhelpful narrative that associates weight and measures of intelligence[5] and policy decisions like barring children's admission to top schools because of their parents' weight.[6]

Publishing this study fuels negative stereotypes that people in bigger bodies lack intelligence—a dehumanizing stereotype that serves to deeply entrench discriminatory practices. There is a growing body of evidence supporting the fact that weight-based discrimination and prejudice are highly damaging[7] and that weight-based discrimination carries both physiological and psychological health risks.[8] Weight stigma has been associated with numerous adverse psychological consequences including depression, anxiety, low self-esteem, and self-isolation.[9] Weight stigma, rather than living in a bigger body, can lead to unhealthy diets and sedentary activity[9] and may also lead to chronic social stress, which has been demonstrated to lead to immunosuppression and increased risk of cardiovascular disease.[10,11] It has also been associated with inequalities in access to education, healthcare settings, employment, and society.[4,9] Given that weight stigma can drive poor health, it must be eradicated[12] and therefore the perpetuation of weight stigma in this paper and its conclusions are unacceptable. Indeed, weight stigma is such a substantial concern that an international committee has issued a joint statement calling for its eradication.[9] In addition, the World Health Organisation (WHO) has recognized the profound consequences of weight stigma and has responded by detailing how the European Region can address weight bias and obesity stigma.[13] The overwhelming evidence of the damage caused by weight discrimination and stigma and the concerns of the international community appear to have been ignored by the authors of this paper, and as a result the true magnitude of the risk to the target population have not been considered.

We note the data for this study came from the Adult Psychiatric Morbidity Survey (APMS), which was undertaken by the University of Leicester, UK on behalf of the National Centre (NatCen) for Social Research in 2007. The survey was commissioned by NHS Digital with funding from the Department for Health and Social Care. The authors state that ethics committee approval was obtained from the Royal Free

Hospital and Medical School Research Ethics Committee. We presume this is for the original 2007 survey but this is not stated. In the interests of transparency, the date and reference number of the original ethics committee approval should be provided in the paper. We have contacted NatCen to ascertain if further permissions to use the data for secondary analysis are needed. Their response indicated that permissions are not needed for the 2007 dataset, but they rely on institutional reviews of research proposals using their data. Given the serious concerns about the paper, it would be useful to determine what, if any, scrutiny by the authors' institutions took place prior to this research taking place.

2 | METHODS

In addition to the ethical concerns outlined above, there are also several methodological issues that we wish to draw to your attention. These issues highlight the critical necessity to carefully consider and address existing stereotypical and scientific assumptions that may negatively impact research directions, methods, and conclusions. Our methodological concerns are divided into three main categories, which we review below: (1) BMI and IQ measurement, (2) the model and the conclusions drawn from it, and (3) Patient and Public Involvement (PPI).

2.1 | BMI and IQ measurement

The authors justify their research question by stating that they are exploring the controversy around BMI and IQ without providing a balanced argument exploring any potential benefits or harms of the stated hypothesis or acknowledging known limitations of the metrics used. It is well established that BMI is a poor indicator of health[14] and the fact that the authors fail to highlight this is a fundamental flaw in their study. The consequences of this underreporting and the variable conditions in which they occur were minimally addressed by the authors, and not addressed in the context of interpretation and analysis.

The paper also fails to acknowledge widespread concerns around IQ testing and its negative impact on people and communities, opting only to acknowledge that familiarity with English may have biased results. The National Adult Reading Test (NART) was originally developed to estimate premorbid intelligence in people with dementia, for neuropsychological testing and research, because it is not possible to assess premorbid IQ directly in these conditions. In a cohort study, in which NART scores of 80-year olds were correlated with IQ tested at age 11, there was only a modest correlation of 0.6.[15] Therefore, the variance in NART scores due to other factors is high, and indeed some of these are likely to be the same structural issues affecting BMI, such as material and social deprivation.

2.2 | The model and conclusions drawn

The analysis crudely explores the association between IQ and BMI metrics, constructing a model with 15 predictors without explicitly considering how the predictors might be related and how they influence any association between IQ and BMI. Furthermore, while the authors have adjusted for individual level variables, there is no consideration of the overwhelming evidence supporting the environmental, social, and structural causes of higher BMI.[16,17] There is no evidence of a direct causal relationship between IQ and weight among those with intellectual disabilities. Adults with severe and profound learning disabilities have been found to have greater instances of 'normal' BMI and underweight, whilst those with mild-moderate learning disabilities were more likely to have overweight and obesity than those in the general population.[18] Amongst those with milder learning disabilities. who may not be known to services (the so called "hidden majority"), factors associated with having low socioeconomic status have been associated with poorer health (including obesity), including material and social deprivation, living in environments in which they did not feel safe, and low income.[19] To propose that a direct, linear relationship between IQ and BMI exists without any further analysis and understanding of the underlying factors, which may link the two is thus incomplete and misleading.

In an attempt to resolve this controversy, Jacob et al. try to control for a large number of potentially related predictors by including them into one large multivariate logistic regression. This approach is controversial and, without a well-informed and often explicit analysis of the relationships between predictor variables, can lead to substantively inaccurate regressions that either obscure or falsely create associations between the predictor variable of interest (IQ) and the outcome variable (BMI).[20–22] With such a large number of predictor variables in their model and with a research topic so rife with potential harm, we believe that the authors should have explicitly used a well-motivated directed acyclic graph (DAG) to warrant the inclusion of every one of the 15 predictor variables included, paying particular attention to stereotypical assumptions and diagnostic biases.[23–25] Simply knowing that a predictor variable might be related both to IQ and to BMI is not enough to warrant its inclusion into a model for an observational study because including it may actually *generate* a confound. For example, it is perhaps reasonable to consider that educational attainment is causally impacted both by IQ *and* by BMI (discrimination at the hands of teachers, parents, and peers impacts ability to progress through educational programs). In this case, where educational attainment is causally impacted by IQ and BMI, it is a collider—and conditioning on it may create a false association between IQ and BMI, known as the Berkson's paradox.

2.3 | Public and Patient Involvement

The authors conducted secondary data analysis from an existing dataset of a survey conducted in the UK in 2006–2007. The current research questions do not appear to have been generated with regard to PPI.[26] PPI is critically important in health research to ensure that research questions are currently relevant to those whose lives may be affected. This research does not address any of the more recently published priority issues

for people with higher BMIs (e.g., https://mrc.ukri.org/research/initiatives/obesity-research/, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/733038/Obesity_workshop_series_to_support_prioritisation_of_research.pdf; https://mrc.ukri.org/research/initiatives/obesity-research/). PPI seeks to democratise research and aims to ensure that researchers are accountable to the public who often directly and indirectly fund research activity. Our collective view, which includes PPI members, is that the topic of this paper would not have been identified as a research priority by people in bigger bodies or members of the public more generally. People with higher BMIs have reported a strong need for research to explore how best to support rather than create further harms reinforcing blame, stigmatisation, and discrimination.

3 | SOCIETAL AND CLINICAL IMPLICATIONS

The paper sets out to explore the risk factors for obesity and states its ultimate purpose is to determine effective prevention strategies. The findings suggest that people with lower IQs could be regularly assessed for obesity, which, as suggested above, would be a highly discriminatory practice and—combined with the fact that most people's weights and BMIs are already frequently screened throughout their lives—a highly ineffective and circuitous practice. There are no suggestions as to how this might be explored in future research and/or implemented into clinical services, although good practice guidelines are available.[27] The authors state that "dietitians, physiotherapists, and general practitioners" can undertake preventative screening work with people with low IQs with no acknowledgement of the complexity of this proposed activity. It is well established that healthcare professionals find it challenging to raise weight management with people,[28] yet their views about the relevance of this research question and the implications for their practice have not been ascertained. The authors also suggest that "IQ may be regularly assessed in specific situations such as the follow up of children with development difficulties or the follow up of adults with psychiatry disorders" without considering the impact of this statement on people in these distinct groups.

Given our numerous, evidence-based concerns, we do not believe the paper meets the journal's criteria for publication. We seek its retraction or, failing that, the publication of this letter alongside it to address the balance.

Yours faithfully

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CONFLICT OF INTEREST

I declare that I have no competing relationships or conflicts of interest. Under ICMJE I led the response, drafted the original letter, revised it according to the feedback I received and submitted it to the journal. I approve of the final version and agree to be accountable for all aspects of the letter.

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Your ref: Jacob L, Haro JM, Smith L, Koyangi A. Association between intelligence quotient and obesity in England *Lifestyle Medicine* 2020. https://doi.org/10.1002/lim2.11

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Lifestyle Medicine Open Access WILEY

REPLY

Reply to Redsell et al

Dear Dr Birrell

Re: Redsell S, Bains KK, Le Broq S, Bucks RS, Byrne-Davis L, Gray L, Hotham S, Hennessy M, Kyle TK, McPherson A, Quigley F, Vicari M, Zinn SR. Concerns regarding "Association between intelligence quotient and obesity in England" and unjustifiable harm to people in bigger bodies. *Lifestyle Medicine* 2021.

We thank Redsell and colleagues for preparing a comment on our important work surrounding the cross-sectional association between intelligence quotient (IQ) and obesity, while adjusting for sex, age, ethnicity, marital status, qualification, employment, income, chronic physical conditions, loneliness, social support, stressful life events, smoking status, alcohol dependence, drug use, and common mental disorders.

1 | METHODOLOGICAL COMMENTS

Our analysis was conducted and reported in accordance with STROBE guidance. The analyses showed that after adjustment for the aforementioned confounders, compared to IQ scores of 120–129, IQ scores of 110–119 (odds ratio [OR] = 1.16), 100–109 (OR = 1.35), 90–99 (OR = 1.26), 80–89 (OR = 1.68), and 70–79 (OR = 1.72) were associated with increased odds for obesity. Furthermore, a 10-point decrease in IQ was associated with a 1.10-fold increase in the odds for obesity. We went on to discuss the findings (i.e., the potential mechanisms that could explain the IQ–obesity relationship) in the context of the limitations of the study and concluded that there was a negative association between IQ and obesity in the UK population.

2 | RISK FACTORS

Correlates of health outcomes and behaviors can either be modifiable (e.g., physical activity level) or nonmodifiable (e.g., IQ). Modifiable correlates inform targets for change in interventions (such as increasing levels of physical activity) and nonmodifiable correlates inform populations who should be targeted for intervention (such as those with a low IQ in obesity prevention).[1] These people with characteristics which may not be modifiable can also benefit from lifestyle interventions as they may be more likely to engage in lifestyle factors, which can lead to adverse health outcomes. In our study, which found that low IQ is associated with obesity, we discuss the potential contribution of lifestyle factors in this association. Identifying both types of correlates in terms of health behavior is essential for successful and targeted intervention. In this context, the present paper perfectly fits into the scope of "Lifestyle Medicine."

3 | PERCEIVED RISK OF HARM

It is not, nor ever has been our intention to fuel inappropriate perceptions of anyone in society. Indeed, we partake in a lot of co-created research with vulnerable groups and their voice is very important to us. We would like it acknowledged though that we do not have control over how research is used. The authors of this letter seem to infer that open access to scientific articles is not appropriate as it may be misinterpreted by parties with a vested interest. We would strongly refute this and choose to publish in open access journals to increase access to ongoing scientific debates.

We never conclude that people with obesity are more likely to have low IQ in our paper. This is a misinterpretation. We do not even show data on the mean IQ levels of people with and without obesity. Second, this is equal to negating all studies that are based on obesity and a potentially stigmatizing condition such as mental health problems or potentially stigmatizing issues such as sexual orientation. In studies that have found that people with schizophrenia are more likely to have obesity for example, would it be possible for someone to criticize or ask for retraction of a paper saying that this topic is dangerous and harmful since people with obesity may be discriminated because they are more likely to have schizophrenia? Data from these kinds of studies would usually be used to further stimulate research on what lifestyle or pharmacological factors are leading to more obesity in people with schizophrenia, so as to improve health status in people with schizophrenia. This is in line with our study aims.

If some media message emerges as a result of a misinterpretation, this would not be a problem of the paper but the interpretation of the journalist.

The authors of the letter have not clarified which journal article the newspaper article on obesity and IQ (citation 5) was based on and how the journalist misinterpreted the content. This is also true for the newspaper article on policy decisions to bar students to top schools because the student's parent is too fat (citation 6). In fact, our paper has nothing to do with parental obesity and it is not clear how this is relevant in the context of IQ.

Furthermore, to justify their claims, the authors of the letter should have shown that previous studies on IQ and obesity directly led to discrimination (and not via a misinterpretation as that is not the fault of the paper but rather the journalist who misinterpreted the data), and that these studies on IQ and obesity had undeniable negative impact on the society. The study topic of IQ and obesity is by no means novel and has existed since more than 40 years ago. Thus, if this study topic were to be harmful, we believe that its impact should be evident by now.

4 | STIGMA

We agree of course that weight stigma has deleterious effects on health. We also agree with the authors of the letter that science is an excellent vector to fight against any type of discrimination. However, based on these claims, it seems that the authors are saying that no studies on obesity and a potentially stigmatizing condition can take place as this can lead to weight stigma. We do not believe that this is likely to happen and omitting these kinds of studies would mean that there will be no data on how to improve health status of people with potentially stigmatizing conditions, which in itself can be discriminatory. If the authors of the letter believe that these studies should be abolished from research, our recommendation would be to contact larger scientific bodies or organizations to disseminate their message and ask for their opinions. In terms of IQ and obesity, as we show below, there is a huge body of literature on this topic, although limited as samples are not nationally representative and key potential confounding variables have not been considered, and thus, contacting all journals and authors of these previous publications may lead to a more balanced view, and requesting a retraction only of our study will probably not lead to any change in practice that the authors of this letter seem to want.

5 | METHODS

We were not sure what this means but the reference provided by Redsell and colleagues does not conclude that BMI is a poor indicator of health but that the diagnostic accuracy of BMI to diagnose obesity is limited. This is a different message. Furthermore, based on the World Health Organization definition, BMI is the parameter used for the diagnosis of obesity. Finally, BMI does have limitations at an individual level. However, it was developed for epidemiological purposes, whereby associations across populations are established. Therefore, the limitations of using BMI do not confound the type of research presented in our paper.

It is incorrect to say the limitations of self-report BMI were not acknowledged. We have openly acknowledged the limitations of self-reported BMI and provided an appropriate reference to substantiate this. The limitations paragraph indicates:

"Second, BMI was based on self-reported weight and height, and it is thus possible that the prevalence of obesity was underestimated in this sample as people tend to underreport their weight.[27]"

A cross-sectional study never assesses causation, as it cannot. We do not understand how "exploring the association between IQ and obesity, not causation" can be a major flaw in the study. Rather, a cross-sectional study that overemphasizes causation is a problem. In our study, this is not the case, as we mention the following in the limitation section:

"Third, this was a cross-sectional study and thus no conclusions about causality or temporality of the association between IQ and obesity can be drawn."

Cross-sectional studies are exploratory in nature commonly used as platforms for future prospective and interventional studies to provide further evidence on causality and direction of associations. They can also instigate future research on the underlying mechanism of a certain association.

It is incorrect to say "there is no consideration of the overwhelming evidence supporting the social and structural causes of higher BMI." Loneliness and social support were included in the analyses, and both loneliness and social support can hardly be considered as individual level variables given that they subjectively and objectively depict the interaction of an individual with his/her environment, respectively.

6 | INTELLECTUAL DISABILITIES

People with intellectual disabilities are out of the scope of the present study. Intellectual disability is traditionally defined as $\geq$2 standard deviations below mean IQ or IQ $\leq$ 70.[2] In our study, participants had IQ scores between 70 and 127. Thus, the study that the authors of the letter cite is not comparable. We are not sure what the authors mean by a direct association but associations after adjustment for various confounders have been found between IQ and obesity as mentioned in the Introduction. Also, adjustment for wealth is included in our study.

Please note that investigations of IQ and obesity are by no means a novel idea and have been extensively studied by various groups for many years since the 1970s and have been present in the academic literature. For example, in 2010, one systematic review collated the literature on the association between IQ and obesity, particularly childhood IQ in relation to adulthood obesity, and included 26 studies.[3] The review concluded that "overall there was an inverse full IQ/obesity association, except in pre-school children. However, after adjusting for educational attainment, full IQ/obesity association was not significantly different. A lower full IQ in childhood was associated with obesity in later adulthood perhaps with educational level mediating the persistence of obesity in later life." We carefully identify this literature among others in the introduction of our paper (see references 6–10).

Redsell et al. state "To propose that a direct, linear relationship between IQ and BMI exists without any further analysis and understanding of the underlying factors which may link the two is thus incomplete and misleading." An association may exist even if there are no adjustments. This is why the phrase "univariate association" exists. There indeed was an association between IQ and BMI in our study and this is not misleading or incomplete as this is the truth. The control variables included in our study are clearly explained. Thus, the readers

are aware of the fact that the association between IQ and obesity in our study is the association when adjusted for these factors and that it is possible that residual confounding may exist due to factors not included in our study. In fact, our study advances the field by including multiple potential confounders, which have not been considered in previous studies on IQ and obesity.

7 | BENEFITS AND HARMS

The benefits of studying this issue are to identify people at high risk of obesity. Based on the argument of Redsell and colleagues, the potential harm that they refer to is caused by a misinterpretation. Any paper can be misinterpreted if read by a nonscholar and it is not normal scientific practice to note that the study may be harmful as someone can misinterpret the data.

8 | NATIONAL ADULT READING TEST

The NART for this study was only conducted for scientific purposes and thus widespread use of IQ testing and its impact on the community is not within the scope of this paper. Furthermore, we do not advocate widespread IQ testing anywhere in the paper.

Interestingly, the paper of McGurn and colleagues that Redsell et al. refer to[4] supports the use of the NART because 0.6 is considered good enough: "These findings validate the NART as an estimator of premorbid ability in mild to moderate dementia."

In addition, another study has shown that a revised version of the NART can be used in people without dementia[5]: "NART-R estimated IQ scores correlated reliably with earlier obtained IQ scores: FS1Q $r = 0.70$; VIQ $r = 0.68$; PIQ $r = 0.61$ (all p's < 0.05)." (Abstract)

"These results represent the first confirmation of the retrospective accuracy of the NART-R in estimating WAIS-R scores across time, a previously untested but critical assumption for clinical application of this approach." (Abstract)

Finally, there are papers derived from the dataset used in our study that use the NART to assess IQ,[6,7] suggesting that this is an accepted proxy in academia.

9 | PPI

This sixth point further emphasizes the misinterpretation of our paper by Redsell et al. Our paper showed that a 10-point decrease in IQ was associated with a 1.10 times higher odds for obesity. Therefore, if PPI was to be conducted then we would select people with lower IQ and not overweight and obesity. We agree that there is great value in PPI. However, Redsell and colleague must try to take a more holistic approach to identifying research priorities of which PPI forms one contributory avenue.

Redsell and colleagues state: "This research does not address any of the more recently published priority issues for people with higher BMIs (for example https://mrc.ukri.org/research/initiatives/obesity-research/)"; in fact, this cited document contains the following statement: "In terms of our remit, obesity's consequences for health are the dominant cause for concern. For example, obesity results in a substantial increase in risk of type 2 diabetes. This means that a balance between approaches – reducing or preventing obesity and breaking the link between obesity and related diseases – is required. An intermediate approach, targeting common points in the link (such as insulin resistance) is also possible." When considering this statement and "preventing obesity" then our paper is addressing this priority in that we are identifying a subset of the population who is at risk of obesity and thus we may wish to target with prevention efforts. Moreover, we know that this population is at greater risk of some obesity-related diseases.

10 | ETHICAL APPROVAL

Secondary data analysis does not require further ethical approval. Furthermore, as mentioned above, Redsell and colleagues have not been able to prove any evidence that this study topic is harmful. Thus, their claim that this study would require further ethical approval due to serious concerns cannot be justified.

11 | SOCIETAL AND CLINICAL IMPLICATIONS

Screening for obesity in people with low IQ is not discriminatory. This is part of preventive medicine. By overemphasizing potential stigma, we believe that the authors of this letter may potentially be fomenting discrimination against people with potentially stigmatizing conditions by leaving them out of health care. This is indeed unethical.

12 | CHALLENGES OF WEIGHT MANAGEMENT

The paper that Redsell and colleagues cite, saying "It is well established that healthcare professionals find it challenging to raise weight management with people [15]" is on child weight management, despite the fact that our study only includes adults. Furthermore, this paper does not say that child management is not possible nor that it should not be done. In contrast, the review identified several facilitators such as healthcare professionals' knowledge or parents seeking help.

13 | WIDESPREAD TESTING

IQ and other related measures are documented in some pediatric and psychiatric practices. We never advocate widespread testing of IQ, so the authors' comment about this is incorrect. Please refer to the text below which can be found in our manuscript:

"Although the present findings provide valuable information on the link between low IQ and obesity, it is important to understand that IQ is a nonmodifiable risk factor that is rarely assessed in the general

population. Therefore, the development of obesity prevention programs focusing on intelligence is difficult to implement. Nevertheless, IQ may be regularly assessed in specific situations such as the follow-up of children with developmental difficulties or the follow-up of adults with psychiatric disorders."

We only suggest strategies under circumstances where data on IQ are available for another purpose.

14 | CRITERIA FOR PUBLICATION

We did not find any evidence-based concerns in the letter by Redsell and colleagues and thus certainly a retraction of this paper is not warranted. In particular, despite their claims "Yet this paper suffers a number of methodological flaws and breaches two ethical principles, namely, beneficence and justice that significantly detract from the soundness of the science." Redsell and colleagues do not provide in the letter any evidence supporting such claims. These are very strong accusations that need to be supported by objective data.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Lifestyle Medicine Open Access WILEY

REVIEW

Lifestyle psychiatry for depression and anxiety: Beyond diet and exercise

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Abstract

There are a range of lifestyle factors which can negatively affect both a person's physical and mental health, and there is increasing evidence that therapeutic lifestyle change can be useful for the prevention and treatment of depression and anxiety disorders. The six core features of lifestyle medicine—regular physical activity, a whole food and plant predominant diet, restorative sleep, stress management, avoidance of substance abuse, and positive social connection—are important foci for mental health providers trying to help patients make meaningful lifestyle changes to improve their well-being. Alongside these elements, there are likely many other aspects of lifestyle important to mental health. The aim of this paper is to provide an overview of five potential lifestyle targets which may play a role in the development and treatment of depression and anxiety, including financial stability, time in nature, pet ownership, materialistic values, and the use of social media. The paper will explore the evidence that these factors contribute to the burden of depression and anxiety in the modern world and will review the potential mechanisms of these effects and clinical implications of interventions targeting these factors.

KEYWORDS
depression, health behavior, healthy lifestyle

1 | INTRODUCTION

Depression and anxiety are major, growing health problems, especially in the developed world. According to the World Health Organization, depression is a leading cause of disability worldwide and a major contributor to the overall global burden of disease.[1] Over 300 million people worldwide suffer from depression, and 260 million people suffer from anxiety disorders.[2] The current first-line treatment modalities for depression and anxiety disorders are psychopharmacology and psychotherapy. Use of antidepressant medication is becoming increasingly common; according to the Center for Disease Control's National Health and Nutrition Examination Survey published in 2017, 12.7% of the US population over the age of 12 had taken an antidepressant medication in the previous month, which represented nearly a 65% increase over a 15-year time frame.[3] Among people receiving treatment for depression in 2015, 80% were prescribed an antidepressant medication and 50% used psychotherapy.[4] Unfortunately, even with adequate trials of antidepressant medication, only a minority of patients achieve remission.[5,6] As a result of the relatively modest effect size of antidepressant medication and the risk of adverse effects, some have even called into question whether antidepressant medications should be prescribed for adults with major depressive disorder.[7] Additional types of treatments that work through a different mechanism are needed for patients who have had an insufficient response to, or are unable to tolerate, current first-line treatments.

Lifestyle factors are a promising avenue for helpful treatments for depression and anxiety. Indeed, a range of lifestyle factors affect both our physical and mental health. In modern societies, many of the diseases causing the greatest morbidity and mortality, such as cardiovascular disease, diabetes, cancer, and depression, are strongly linked to lifestyle choices.[8] In his 2012 paper entitled "Depression as a disease of modernity" Hidaka[9] looks at the aspects of modern culture which contribute to the increasing prevalence of depression and concludes that "modern man would likely be much more resilient to the toils of living if he were physically fit, well-rested, free of chronic disease and financial stress, surrounded by close family and friends, and felt pride in his meaningful work."[9(p9)]

Given the importance of lifestyle factors to depression and anxiety, it is unsurprising that there is increasing evidence that lifestyle recommendations may be useful for the prevention and treatment of mental illness.[10–12] Lifestyle medicine is a field of medicine which aims to prevent and treat chronic disease through modification of lifestyle behaviors. The American College of Lifestyle Medicine defines six core features of a healthy lifestyle: regular physical activity; a whole food, plant predominant diet; restorative sleep; stress management; avoidance of substance abuse; and positive social connection.[13] While lifestyle medicine often focuses primarily on preventing and treating physical illnesses, especially cardiovascular and metabolic diseases, there is strong evidence that these lifestyle factors also impact depression and anxiety.[10] In fact, in one Australian study, patients with clinical depression rated exercise as the most effective intervention.[14]

This focus on therapeutic lifestyle change for the prevention and treatment of mental illness has been termed "lifestyle psychiatry."[10,15] Alongside the well-established tenets of lifestyle medicine, the field of lifestyle psychiatry explores other elements of lifestyle and behavior which contribute to mental health. The aim of this paper is to provide an overview of five lifestyle factors outside of the core tenets of lifestyle medicine, which may be linked to risk for depression and anxiety. These five lifestyle areas include financial stability, time in nature, pet ownership, materialistic values, and the use of social media. While there are numerous elements of a person's lifestyle which may affect mental health, these five areas were chosen out of the collection of important lifestyle factors discussed in the papers by Hidaka,[9] Walsh,[12] and Sarris et al.[11] The authors went through the following process to select the five specific areas chosen to review in this paper. First, we compiled a list of all aspects of lifestyle discussed in these three papers, then removed the six core lifestyle medicine features along with topics that could be seen as a subset of one of the core features (i.e., mindfulness meditation as a means to manage stress). We then eliminated the topics that would require large-scale social change (i.e., inequality, capitalistic values, secularization) as these would be difficult to impact through working with individual patients. Lastly, the five topics covered in this paper were chosen from the factors that remained based on a preliminary review of the literature and what seemed to be most relevant and amenable to intervention based on the authors' clinical experience. This paper will explore the evidence that these five factors contribute to the burden of depression and anxiety in the modern world and will assess the efficacy and clinical implications of interventions targeting these factors.

2 | REVIEW

2.1 | Financial stability

Finances are a major source of stress for many people. A 2016 study found that 23% of Americans and 36% of American millennials reported experiencing a "debilitating degree of stress" related to their finances.[16] With the spread of consumer culture and easy access to credit, people are spending money they do not have on items they cannot afford. Rates of debt are quite remarkable in many countries; in the United States the amount of consumer credit card debt per household tripled from the 1980s to the early 2000s.[17] Since then, accumulation of debt continues to climb precipitously; median household debt in the United States was $50,971 in 2000 and nearly tripled to $137,063 in 2018.[18]

Unfortunately, the spread of mass consumption has come at a major psychological cost, as debt and financial hardship have been found to have strong ties to mental illness. Overall, a higher ratio of household debt to assets is associated with higher rates of stress and depression and worse general health.[17] A meta-analysis by Richardson et al.[19] in 2013 found that debt increased the likelihood of depression nearly threefold (odds ratio (OR) = 2.77) and increased the odds of neurotic disorders such as clinically significant anxiety over threefold (OR = 3.21). When we look specifically at unsecured debt, such as consumer credit card debt, we see an especially strong relationship with poorer mental health[19]; however, even home mortgage debt may play a role. The onset of mortgage debt is associated with a negative impact on mental health,[20] and a ratio of housing cost to income >28% predicts lower psychological well-being.[21] An analysis of the British Health Panel Survey data in 1991–2003 found that housing payment problems or arrears negatively impacted mental health more than either unemployment or widowhood/divorce.[22,23]

Debt and financial hardship appear to have an especially strong association with suicidal ideation and suicide completion. The meta-analysis by Richardson et al.[19] mentioned earlier found a strong association between debt and suicide completion (OR = 7.9). A study of the general population of the United Kingdom in 2011 found that debt increased the risk of suicidal ideation in a dose–response fashion.[24] A case-control study in China of 85 suicide completers compared to 85 community controls found that "unmanageable debt" was associated with suicide (OR = 9.4), even when controlling for income, employment, psychiatric conditions, and family suicide history.[25] Furthermore, a different case-control study in China of 150 suicide completers compared to community controls estimated that 23% of suicide was attributable to debt.[26]

Although these examples show a strong association between debt and reduced mental health, the direction of the effect is less clear; does debt cause depression, anxiety, and suicidal ideation, or do people suffering from mental illness have a higher likelihood of

accumulating debt? Available evidence suggests that this connection runs in both directions. A longitudinal study of the effect of financial strain on depression among unemployed persons and their spouses in the United States in 1996 concluded that the direction of influence runs from financial strain to depressive symptoms.[27] A more recent longitudinal study in 2006 looking at the connection between socioeconomic position and common mental disorders found that financial strain at baseline was associated with an increased occurrence of major depression at follow-up.[28] On the other hand, other studies that have concluded that the direction of influence runs in the opposite direction. A longitudinal study of mothers with young children in the United Kingdom in 2001 concluded that poor mental health increased the likelihood of worry about debt, as the effect of worry about debt on later depression disappeared when baseline depression was controlled for.[29] Additionally, a study of university students found a bidirectional relationship between financial difficulties and global mental health.[30]

What is it about financial difficulties that leads to the development of problems with depression and anxiety? When the meta-analysis by Richardson et al.[19] looked into this question, they found that three studies concluded that worry about debt rather than debt in and of itself led to a reduction in mental health, while two other studies concluded that it was financial strain rather than debt that had the effect.

If it is subjective stress about debt rather than objective measures of debt that leads to poor mental health, then psychological interventions may be effective in attenuating the connection between debt and reduced mental health.[19,31] Richardson et al.[19] conclude that interventions such as cognitive behavioral therapy may be able to improve mental health by reducing worry about finances and catastrophizing. A study in the United States in 2014 concluded that perceived control over one's financial circumstances predicted the absence of depressive symptoms. The authors recommend that mental health practitioners consider emphasizing psychosocial strategies to increase perceived control over finances such as money management skills and financial education.[21] While there are few studies specifically looking at the health effects of financial education programs, one such study conducted in the United States found that participants of a debt management program experienced improvements in their financial well-being and perceived health status.[32]

2.2 | Time in nature

Many people now spend the vast majority of their time indoors, surrounded by urban, built environments. This isolation from nature is associated with stress and poorer mental health.[33,34] It is becoming increasingly recognized that immersion in nature appears to offer benefits for reducing symptoms of depression and stress. There are a number of theories as to why this may be the case; time spent in nature may help to alleviate mental fatigue, green spaces offer a setting for relaxation and socializing, and access to nature may be associated with increased physical activity.[35,36] This paper looks at the benefits of immersion in nature, views of nature, and access to green space for depression, stress, and overall mental health.

Spending time in nature can improve the mood of people suffering from depression. A 2012 study of individuals with depression assessed the mood and short-term memory of study participants before and after walks in either nature or an urban setting. Compared to walking in an urban setting, going for a walk in nature led to an improvement in mood and an increase in memory span.[37] A meta-analysis by Roberts et al.[38] in 2019 looked at 33 studies to determine the effect of short-term exposure to nature on depressed mood; overall they found a small effect, though noted that the studies included were of low quality.

One way immersion in nature can lead to psychological restoration is by reducing physiological arousal, as is demonstrated by a number of studies comparing the recovery from stress in natural versus urban environments.[39–42] A 2010 study in Japan compared the physiological effects of immersion in a forest versus a city environment. The investigators found that the participants who engaged in a forest walk developed lower concentrations of cortisol, lower heart rate, lower blood pressure, and greater parasympathetic nerve activity compared to participants who walked in a city environment.[40] A similar study conducted in the United States found that in addition to reducing their blood pressure, participants instructed to walk in a nature reserve rated their mood to be improved and anger decreased following the walk, whereas the opposite pattern was seen for participants walking in an urban environment.[41] In a 1991 study, participants watched a horror film and were then exposed to natural versus urban scenes on videotape. Participants who were exposed to scenes of the natural environment had faster and more complete recovery following the stress of the horror film when looking at a number of markers of physiological stress, including heart rate, muscle tension, skin conductance, and systolic blood pressure.[42]

Simply having a view of nature can benefit a person's mental health. A study in 1984 compared the hospital course of a group of patients undergoing gall bladder surgery. This study found that the patients who had a view of trees outside of their hospital room window spent less time in the hospital (one day less), required fewer pain medications, had fewer postoperative complications, and reported better mood compared with patients recovering in a room with a view of a brick wall.[43] A similar study conducted in a prison environment in 1981 looked at the effects of nature views for prison inmates; inmates with views of nature from their cell window had a lower frequency of stress-related health complaints, including digestive illness and headaches, and fewer overall sick calls.[44]

In addition to the benefits of viewing nature in stressful environments, access to green space within one's neighborhood also seems to offer benefits for preventing depression and lowering one's stress levels. In a systematic review by Gascon et al.[45] in 2015 looking at the mental health benefits of exposure to nature in residential areas, the authors found that among 18 relevant studies, most observed enhanced mental health with increasing surrounding greenness.[45] A study in the Netherlands in 2010 looked at the moderating effects of nearby green space on perceived health. The authors found that study participants with a high amount of green space within 3 km of their home were less affected by stressful life events compared to participants with a low amount of green space nearby.[46] A population-level

study in the United States in 2014 looked at the relationship between green space and mental health outcomes in a variety of urban to rural environments. They found that neighborhood green space was consistently associated with lower levels of depression, anxiety and stress, with depression showing the strongest relationship.[47] Not only is the association between increased access to green space and improved mental health statistically significant, it is also clinically meaningful; the difference in average depressive symptoms between people living in an area with 100% tree canopy compared to people living in an area with no tree canopy is larger than the difference in depressive symptoms between an uninsured population versus a population with private insurance.[47] The benefits of environmental green space is further quantified in a 2013 ecological study in New Zealand which found that every 1% increase in the proportion of useable or total green space near a person's home was associated with a 4% lower rate of anxiety or mood disorder treatment.[48]

One of the theories for why increased access to green space leads to mental health benefits is that it leads to greater physical activity. A 2013 study in Australia looking at the association between green space and psychological distress found that green spaces promote physical activity, and the mental health benefits of natural environments are contingent upon the population leading a more active lifestyle. In their study, increased access to green space appeared to benefit mental health only among the more physically active segment of their study population.[49] In a 2013 study using New Zealand Health Survey data, physical activity only partially explained the relationship between access to nature and improved mental health.[50] Aside from the mediating role that physical activity likely plays in the association between access to nature and mental health, there is also a field of research into "green exercise" which compares the benefits of exercise in natural versus built environments. A large epidemiological study in Scotland from 2013 found that physical activity in natural environments was associated with enhanced mental health compared to physical activity in other environments; they specifically found that people who exercised in woodlands or forests had half the risk of poor mental health compared to people who did not use natural environments for exercise, even when controlling for overall amount of physical activity.[51]

One final way to look into the mental health benefits of immersion in nature is by examining the influence of gardening and horticulture therapy. Gardening has a long history of use as a therapeutic activity for people experiencing mental health difficulties; as early as the 1800s, psychiatric institutions in the United States and Europe used horticultural activities as a form of therapy for their patients.[52] A meta-analysis by Soga et al.[53] in 2016 looked at 22 studies examining the effects of gardening on health. Overall, they found that most studies reported a positive effect of gardening on health outcomes, and none reported a significant negative effect. Even a short period of exercise in gardens led to reductions in depression and anxiety symptoms. When they looked specifically at seven studies focusing on daily gardeners, they found that participants who were daily gardeners had lower stress levels, higher life satisfaction, and overall better general health than did nongardeners.[53] Soga et al.[53] detail several pathways by which gardening promotes health, including enhancing physiological recovery from stress, encouraging physical activity, promoting interaction with one's community, and by supplying people with fruits and vegetables. Overall, we see that time in nature, even in one's own backyard, can offer substantial benefits for one's physical and emotional well-being.

2.3 | Pet ownership

Healthy, supportive relationships are vital to a person's well-being, and in fact, forming and maintaining relationships is one of the six tenets of lifestyle medicine as defined by the American College of Lifestyle Medicine.[13] One of the most notable studies to demonstrate the importance of lifestyle factors for health and happiness throughout a person's life is the Harvard Study of Adult Development, a longitudinal study begun in 1938 that continues through the present day. The researchers of this study have found that relationships have a powerful influence on a person's health, and that close relationships are key to keeping people happy throughout their lives. In fact, they've found that loneliness is just as bad for a person's health as smoking and alcoholism.[54] Unfortunately loneliness is all too common, with three in five Americans (61%) reporting being lonely in a 2019 study by Cigna.[55] Loneliness takes a toll on both a person's physical and mental health and is associated with an increased risk for early mortality (OR = 1.26).[56]

While we know that social support is crucial for a person's well-being, the question we are addressing here is whether a person's pets can fulfill this need. Many people in modern Western cultures have very close relationships with their pets. In fact, a large poll conducted by the Associated Press in 2009 found that 50% of American pet owners view their pet "as much a part of the family as any other person in the household."[57] A study in 2011 looked into the degree to which pets can fulfill a person's social needs. When the authors looked at ratings of overall social support, they found that support by pets was statistically equivalent to the amount of overall support provided by a person's parents or siblings; the only group that provided significantly more support than pets was a person's best friends. This relationship with improved mental health persisted even when controlling for human sources of social support, indicating that a person's pets can make a unique contribution to the fulfillment of a person's need for social support above and beyond the effects of human sources.[58] Although we see that pets can provide an important companionship role regardless of a person's human social capital, the social support that pets can provide may be even more important for people with fewer close and supportive human relationships. A study in 1999 looked at the effects of pets on depression among men with HIV. They found that overall, men with AIDS who owned pets reported less depression than those who did not own a pet, and this benefit of pet ownership was principally seen among men with fewer close confidants.[59]

The relationships people have with their pets are beneficial for well-being and mental health. A 2017 study of the relationship between dog-ownership and depression in people living with HIV summarized the improved psychological outcomes associated with dog ownership,

including less depression and loneliness and improved general sense of well-being, as well as the facilitation of social interactions and building social networks.[60] A 10-month prospective study in England looked at the changes in behavior and health status of a group of adult participants following the acquisition of a pet, as compared to a control group with no pets. While the control group exhibited no significant health or lifestyle changes over the course of the study aside from a small increase in walking, the pet-acquiring group showed significant improvements in psychological well-being over the first 6 months, an improvement which was maintained in the dog-owning group through the end of the study.[61] In a 2001 study in the United States, a group of hypertensive adults in high-stress professions were randomized to start lisinopril and acquire a pet, or to just start lisinopril. The investigators looked at the effect of pet ownership on blood pressure responses to psychological stress and found that ACE inhibitor therapy lowered only resting blood pressure, whereas pet ownership lowered blood pressure response to stress.[62] A 2018 study looked at the effects of pet acquisition in patients with treatment-resistant major depressive disorder and found that the group of patients who took the suggestion to adopt a pet had higher response and remission rates compared to the control group. The authors of this study concluded that pets can be an effective adjuvant to antidepressant medications.[63]

One question that remains is whether or not there is a difference between dogs and cats in terms of the mental health benefits they can provide for their owners. A study in 1991 which looked at the change in behavior and health status of adults following acquisition of a pet found that 50% of dog owners felt that their pet had made a major difference to their lives, whereas only 37% of cat owners reported feeling the same way.[61] However, what may be more important than the type of pet is the strength of the relationship between a person and their pet. A study in 1999 looking at the benefit of pets in preventing depression for men with AIDS found that there was no significant difference between dogs and cats when taking into account the strength of the affective bond a pet owner felt toward their pet.[59]

2.4 | Materialistic values

The spread of consumer culture has resulted in a higher value being placed on the acquisition of material goods. A paper by Richins and Dawson[64] in 1992 defines materialism by describing three main facets—that the acquisition of material possessions is a central focus of a person's life, a main source of life satisfaction, and seen as a marker of success. This focus on the importance of acquiring conspicuous consumer goods appears to be on the rise among young people.[65,66]

Given the rapid spread of consumer culture, it is problematic that materialism has been consistently associated with lower levels of life satisfaction.[67] In fact, some have hypothesized that this shift in the value system of our society is one aspect that explains the increasing prevalence of mental health concerns. In his 1990 paper entitled "Why is there so much depression today?," Seligman[68] notes that the prevalence of depression among young Americans in the late 20th century was roughly 10 times greater than it was 50 years earlier, prior to the cultural shift in production and consumption that followed World War II. He goes on to further explore the effect of this cultural shift by comparing rates of depression in modern societies to those in traditional, nonconsumerist societies still alive and well in the modern world, such as the Old Order Amish, who at the time had rates of major depressive disorder one-fifth to one-tenth of the rate in Baltimore, just a hundred miles away.[68,69]

The impact of materialistic values on mental health appears to be quite broad. In their 1992 study, Richins and Dawson[64] found that materialism was negatively correlated with all aspects of life satisfaction, including satisfaction with income, standard of living, family life, and friends. A meta-analysis of 151 studies by Dittmar et al.[65] in 2014 concluded that the more strongly people endorse materialistic values, the poorer their personal well-being; this detrimental effect was seen in a variety of domains including negative self-appraisal, lower life satisfaction, and increased rates of depression and anxiety. The authors of the meta-analysis postulated that the link between materialism and well-being may be mediated by the negative effect of materialistic values on a person's ability to fulfil their need for competence, autonomy, and strong interpersonal relationships. This occurs because the focus on acquiring money and possessions, as well as personal image, crowds out pursuits that are more likely to lead to greater well-being in the long run.[65,70] In addition, gratitude also appears to be an important mediating factor between materialism and reduced well-being; by focusing on what they do not yet have, it is difficult for materialists to appreciate the positive in their lives.[67]

While studies have found that well-being decreases as people become more materialistic in their aspirations over time, there is also evidence that the reverse can be true as well.[71,72] Three longitudinal studies conducted in the United States and Iceland found that among participants whose priorities shifted away from materialistic values and goals over time, their well-being improved.[71] An interventional study of adolescents found that a three-session financial education intervention that focused on teaching participants healthy financial habits and about the impact of advertising and consumer culture was successful in decreasing adolescents' materialism. This decline in materialism was associated with a significant increase in self-esteem.[71] In addition to financial education as a means of reducing materialistic values, a number of studies have also pointed to gratitude as a potential target for improving life satisfaction[67,73–75]; Tsang et al.[67] suggests that an intervention such as a gratitude journal may be one such possibility to help individuals with highly materialistic values. This theory was tested in a 2018 study which found that a gratitude journal intervention lead to a reduction in materialism and an increase in generosity among adolescents as compared to a control group of adolescents who were asked to journal about their daily activities.[76] Others have pointed to mindfulness and a focus on promoting awareness of the present moment without judgement as a potential tool to help individuals with highly materialistic values improve their mental health and gain life satisfaction.[75,77] A 2019 study conducted in Germany found that a mindfulness-based intervention led to a decline in materialistic values among study participants, as well as a

greater sense of well-being among the student subset of their study population.[78]

2.5 | Social media and smartphone use

Smartphone use is becoming ubiquitous in modern society. In 2019, 81% of American adults owned a smartphone, and rates were even higher for younger adults; 96% of adults ages 18–29 owned a smartphone, and 92% of adults ages 30–49.[79] Rates of smartphone ownership are also increasing around the world. The global median rate of smartphone ownership was 59% in 2017.[80] Smartphones serve many functions, and they are now commonly viewed as a necessity in the lives of individuals. Even in 2014, when just over half of American adults owned a smartphone, nearly half of smartphone users said that they "couldn't live without" their smartphone.[81] One common use of smartphones is to access social media platforms. Like smartphone use overall, use of social media is increasingly prevalent in both the United States and around the world. In 2019, 72% of American adults reported use of at least one social media platform. Similar to smartphone use, these rates are especially high among young adults, with 90% of Americans ages 18–29, and 82% of Americans ages 30–49 using social media.[82] Among American Facebook users, nearly three-quarters (74%) visit the site at least daily, and just over half (51%) report visiting the site several times per day.[82] Globally, over half of people in the 39 countries surveyed by the Pew Research Foundation use social media,[80] and the average amount of time spent on social media by users worldwide was 2 hours and 22 minutes per day.[83]

There are numerous potential benefits of smartphone use, including productivity enhancement through features such as calendars, reminders and email, relaxation and entertainment, and social interaction.[84,85] Smartphones are frequently used to facilitate social engagement, such as through text messaging, calling, and accessing social media platforms, and consequently smartphone use has the potential to help build social capital.[84] Research has shown that use of social media platforms such as Facebook can help college students obtain social support[86] and may be especially important for facilitating the formation of social ties for users with low self-esteem.[87] Among senior citizens, Facebook use can help social media users to maintain their existing social networks, especially with geographically distant friends and family members, and facilitate intergenerational communication.[88,89] Overall, seniors who use Facebook have increased frequency of contact with their family and friends and are more likely to be satisfied with their social interactions that those who do not use Facebook.[88,90,91]

While there are potential benefits to gain from smartphone and social media use, there are also a number of ways excessive smartphone and social media use has been found to be harmful. Excessive smartphone use is associated with worse physical fitness, musculoskeletal pain, sleep impairments, traffic and pedestrian accidents due to distracted drivers, interference with school or work, and reduction of real-life social interaction.[84,92] A number of studies have also demonstrated an association between depression and anxiety with smartphone and social media use. For example, a survey study of University students in Turkey found that smartphone use severity was positively correlated with depression (r = 0.267) and anxiety (r = 0.276).[92] A study of nearly 2000 American adults in 2014 found that participants in the highest quartile of total time per day spent on social media had significantly greater odds of having depression compared to those in the lowest quartile (adjusted odds ratio = 1.66).[93] A systematic review by Elhai et al.[94] in 2017 looked at the relationship between problematic smartphone use and depression and anxiety psychopathology. Overall, depression severity was associated with smartphone use with correlation coefficients ranging from 0.3 to 0.5, and anxiety was also associated with smartphone use, although with smaller effect sizes (correlation coefficients averaging 0.2).[94]

The impact of social media and smartphone use on mental health appears to be more related to the nature of a person's use of the technology, rather than simply the frequency and duration of use.[95–97] Social smartphone use (i.e., calling, texting) and active use of social media (i.e., sending messages, commenting on friend's posts) is associated with positive well-being in users.[95,96] When social media is used to communicate directly with other individuals, especially when sending personalized messages as opposed to "one-click communication," it can help users to increase their social capital and to feel less lonely.[98,99] On the other hand, passive consumption of social media, such as scrolling through a media feed without interacting, correlates to feelings of disconnectedness and depression.[99,100] In a 2017 study looking at the effects of social versus process smartphone use on depression and anxiety symptoms, the authors describe how individuals without depression and anxiety were more likely to engage in social smartphone use, thereby taking advantage of the adaptive features of their smartphone to establish and maintain social relationships, whereas individuals with depression and anxiety were more likely to engage in process smartphone use, such as news consumption and entertainment, which can facilitate social withdrawal.[96]

The majority of studies looking at the association between smartphone/social media use and mental health are cross sectional, and therefore the directionality of the association between use of these technologies with depression and anxiety is not clear. It is likely that this relationship is bidirectional, and there are a number of hypotheses for the mechanism of the effect in either direction.[93,94,96,101] Individuals with social anxiety may find online social interaction less stressful than in-person interaction and may then compensate for their discomfort in face-to-face interactions by socializing excessively online.[101–103] On the other hand, anxiety can lead to social avoidance, and people with higher levels of anxiety have been found to prefer process smartphone use (web surfing, news consumption), over social smartphone use, thereby avoiding social interaction altogether.[96] Both depression and anxiety can lead to rumination, which can lead to excessive reassurance seeking by habitually checking one's phone for social notifications.[101] Further mediators between depression and excessive smartphone and social media use include decreased behavioral activation, making people less likely to participate in in-person social engagements, and a diminished sense of self-worth,

which then leads people to pursue social media interactions for validation.[93,104]

Excessive and maladaptive use of smartphones and social media may also lead to worsening symptoms of depression and anxiety through a variety of mechanisms. Excessive use of one's smartphone at night can impair sleep, both through active use while one should be sleeping and also by way of blue light from the screen making it more difficult to fall asleep.[94,97] Social media also enables individuals to closely follow the social escapades of their friends, which can lead to feelings of victimization and exclusion when one sees their friends socializing without them.[97] Frequent users of social media may substitute online interactions for face-to-face social interactions,[105] and excessive engagement with social media and smartphones can lead people to isolate themselves and neglect to engage in activities important to psychological health, even beyond in-person social interactions.[84] Perhaps one of the most important ways social media can lead to symptoms of depression is by way of increased upward social comparison.[95,97,106] Exposure to the highly curated and idealized portrayals of peers on social media can lead to feelings of envy and the belief that others are leading happier, more successful, and more connected lives.[93,105] There are a number of studies supporting this idea about the harms of increased social comparison; a study of college students found a direct link between the amount of time spent on Facebook per day and social comparison, which was associated with lower self-esteem and negative mental health outcomes.[107] College students who spent more time on Facebook each week were more likely to agree that others had better lives than themselves.[108] A German study of social media users found that study participants shown profile pictures of physically attractive individuals subsequently had more negative ratings of their body image than those shown pictures of less attractive individuals, and men shown profiles of more successful individuals rated the divergence between their current career status and their ideal career status as greater than men shown the profiles of less successful individuals.[109]

While there is no one "right answer" with regard to the ideal use of smartphone technology and social media platforms, we see that the way individuals use these technologies is important for mental health outcomes. In their 2018 study of problematic smartphone use, Elhai et al.[110] recommend using strategies to improve emotion regulation such as distress tolerance skills and mindfulness-based cognitive behavioral therapies. These strategies could help individuals manage excessive technology use by learning to process rather than avoid negative emotions. Mindfulness-based strategies may also help smartphone and social media users to become more aware of the beneficial and deleterious effects of their current use patterns on their mental health and develop more adaptive use patterns in line with their values and priorities.[110] Beyond encouraging individuals to change the way they use social media, some researchers have looked into the effects of limiting social media use entirely. One such study among college students in 2018 found that study participants asked to limit their use of social media to 30 minutes per day had significant reductions in loneliness and depression compared to students who continued their usual social media use.[111]

3 | CLINICAL CONSIDERATIONS

There are a range of strategies available to mental health providers looking to help their patients make therapeutic lifestyle changes. These approaches need to be individually tailored to the patient and the practice, based on such factors as the patient's preferences and readiness for change as well as the resources available to the provider. A lifestyle psychiatry intervention could range in intensity anywhere from a quick review of standard lifestyle recommendations after a primary care visit to enrolling in a systematic lifestyle program for mental health similar to programs that currently exist for treating cardiovascular disease and type II diabetes mellitus.[112–114] One randomized controlled trial conducted in Spain looked at the effect of giving patients with depression a list of four lifestyle recommendations. The active treatment group was given an envelope with a sheet of paper listing specific recommendations regarding diet, exercise, sunlight exposure, and sleep patterns, whereas the control group received the same envelope but with the recommendation to make choices with regard to these lifestyle factors that they thought might make them feel better. Even with just this simple intervention, the researchers found a significant improvement in the depressive symptoms in the active group compared to the control group; not only were many more participants in the active group able to achieve remission from depression, but fewer participants in the active group required an increase in dose of their antidepressant medication and more were able to decrease the dose compared to participants in the control group.[114] Studies like this show us that even small steps can make a big difference in the effective treatment of psychiatric conditions. While some physicians may feel at times that trying to convince patients to make behavioral change is futile, research shows that physician's advice regarding diet and exercise does make a different in motivating patients to make lifestyle changes.[10]

The five lifestyle factors discussed in this paper could similarly be incorporated into clinical practice in a number of different ways. Some of the elements could be included in standard lifestyle recommendations to all patients. For example, in addition to informing patients about the benefits of a healthy diet and adequate physical activity and sleep, a mental health provider could also include recommendations about spending time in nature, or the benefits of keeping a gratitude journal. For some of the factors discussed in this paper, it would be important to first assess the relevance to a specific patient in order to tailor advice to their specific situation. An example is pet ownership—some patients already have pets, while others do not enjoy animals or do not have the means to care for a pet, so advising a patient to consider adopting a pet would only be helpful for a subset of patients. Another example would be the need to assess a patient's current use of social media before giving recommendations, as there is not a one-size-fits-all answer when it comes to the optimal use of social media. Lastly, it may be unrealistic for a mental health provider to be the one to provide specific guidance to a patient, and therefore they could instead play the role of screening and referring patients to appropriate resources. For example, if a patient has significant financial stress it may be more helpful and reasonable to refer them to a debt counselor

TABLE 1 Summary of key findings in review of five lifestyle factors likely to influence mental health

Lifestyle factor	Summary of highlights
Financial stability	- Nearly a quarter of Americans experience a "debilitating degree of stress" related to their financial situation.[16] - Debt and financial hardship are associated with an increased risk of depression and suicide.[17,19] - Stress about debt, rather than objective measures of debt, influences the roll of financial strain on mental health.[19,22,25]
Time in nature	- Having a view of nature can improve mental and physical health.[33,43,44] - Access to greenspace within one's neighborhood is associated with better mental health and less harm from stressful life events.[45–48] - Time in nature fosters greater stress reduction than time spent in urban environments.[40–42] - Exercise in nature offers enhanced mental health benefits compared to exercise performed elsewhere.[51]
Pet ownership	- Many people consider their dog or cat to be a member of their family.[57,58] - Acquiring a pet is associated with improved psychological well-being, and can lower blood pressure response to stress.[59–62] - Pets can provide a level of social support comparable to a person's parents or siblings.[58] - Affective bond with a pet, not the species of pet, is most important in determining the impact of a dog or cat on the owner's well-being.[59]
Materialistic values	- Increased focus on acquiring material goods as marker of success is hypothesized to be a factor contributing to rise in rates of depression.[68] - Materialistic values are negatively correlated with life satisfaction.[64,65,67,115] - Focus on acquisition of conspicuous consumer goods crowds out pursuits likely to enhance well-being in the long run.[65,70] - Interventions to reduce materialism can include financial education, gratitude, and mindfulness.[67,71,73–75]
Social media and smartphone use	- Social media and smartphone use are quickly becoming nearly ubiquitous.[79,80,82] - Potential advantages include enhancing productivity, providing entertainment, facilitating social interaction.[84–89,116] - Downsides of excessive or maladaptive use include worse physical health, sleep impairment, interference with other responsibilities, and reduced real-life social interaction.[84,92] - An especially problematic aspect of social media use is increased upward social comparison; constant exposure to the "highlight reel" of friends and acquaintances leads to envy and lower self-esteem.[93,95,97,105–107]

than to attempt to provide personal finance guidance during an appointment.

4 | SUMMARY

Lifestyle medicine is a growing field which aims to help patients prevent and treat chronic diseases by developing healthy lifestyle habits. While the focus of lifestyle medicine is often a person's physical health, the core tenets of lifestyle medicine also apply to the prevention and treatment of mental illnesses. The first line treatments for mental health concerns such as depression and anxiety remain psychopharmacology and psychotherapy; however, there is growing evidence of the importance of therapeutic lifestyle change for the treatment of these conditions.[10,11,15]

While research into the elements of a person's lifestyle most important for mental health continues to expand, it is likely that the six core features of lifestyle medicine will similarly be the lifestyle features with the greatest impact on mental health and overall well-being. These six factors include a plant predominant diet, regular physical activity, restful sleep, stress management, avoiding risky substance use, and maintaining supportive relationships.[13]

In addition to these six well-established tenets of Lifestyle Medicine, there are likely many other aspects of a person's lifestyle choices that influence their well-being and play a role in the development and also treatment of depression and anxiety. The five areas reviewed in this paper include financial stability, time spent in nature, pet ownership, materialistic values, and social media and smartphone use, and are briefly summarized in Table 1. There are additionally numerous other aspects of one's lifestyle choices likely to play a role in supporting or impeding well-being, such as recreation, service to others, gratitude, having a sense of purpose, and spirituality, which could be targets of lifestyle psychiatry research going forward.

5 | CONCLUSION

The burden of morbidity related to depression and anxiety is increasing around the world, and the current first-line treatments of psychopharmacology and psychotherapy are in many cases not sufficient to meet the needs of patients suffering from these illnesses. There is growing evidence that lifestyle factors play a role in the development, and also the treatment of these disorders, and there should be a focus among mental health providers in trying to help patients make therapeutic lifestyle changes. These lifestyle interventions should include the core features of lifestyle medicine, such as diet, exercise, and stress management, but in addition mental health providers should consider addressing other lifestyle factors including financial stability, time in nature, pet ownership, materialistic values, and the use of social media. Not only would an increased focus on behavioral change be

likely to improve patient's mental and physical health outcomes and reduce the overall costs to the medical system, there could also be secondary benefits as healthy behaviors can spread extensively through social networks. There is a growing need for innovative, integrative approaches for the management of depression and anxiety. Lifestyle psychiatry advocates can both promote therapeutic lifestyle interventions within the current mental health system and also develop systematic lifestyle programs for mental health.

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REVIEW

The metabolic signatures of cardiometabolic diseases: Does the shared metabotype offer new therapeutic targets?

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Abstract

Cardiometabolic diseases (CMDs) are the most common, noncommunicable diseases that claim many lives every year. CMDs have great impact on public health, often driving the attention of healthcare resources to prevent and treat them. CMDs include cardiovascular diseases, type 2 diabetes mellitus, metabolic syndrome, and obesity. Deep understanding of the root causes and pathogenic factors of CMDs would help in their effective prevention and treatment. Metabolomic profiling of biosamples usually sheds light on the metabolic biomarkers and the involved pathways. Metabolomic analysis to identify CMDs metabotypes revealed that they share similar metabolic signatures and metabolic pathways. These metabolic pathways may indicate the presence of insulin resistance, mitochondrial dysfunction, low-grade inflammation, and dysbiotic gut microbiota. This study is aimed to review the literature on the common metabolic biomarkers of CMDs as well as the shared pathways that can be targeted by dietary interventions and pharmacologic treatment.

KEYWORDS
heart diseases, inflammation, insulin resistance, metabolic diseases, metabolomics, microbiota, mitochondria

1 | INTRODUCTION

Noncommunicable diseases (NCDs) are chronic diseases which account for 71% of yearly global deaths.[1,2] They include cardiometabolic diseases (CMDs), cancers, and chronic respiratory diseases. Due to their great burden on global public health, preventing and treating NCDs have gained the attention of global public health and healthcare entities.[3,4] Among all NCDs, CMDs account for most of global deaths caused by NCDs.[1,2] CMDs are interlinked diseases which include cardiovascular diseases (CVDs), such as coronary artery disease (CAD), heart failure (HF), hypertension, dyslipidemia and stroke, as well as metabolic syndrome, obesity, and diabetes mellitus (DM).[5,4] Besides their high mortality rate, CMDs have a detrimental effect on the immune system which affects the outcome of other diseases such as cancers and infections.[6–9] With the current available data, it has been well documented that patients suffering from CMDs have a high risk for coronavirus disease 2019 (COVID-19), and they may suffer from severe outcomes. [9–12] This has increased the global concern on advancing efforts for preventing and treating CMDs. [12,13]

CMDs have a heterogenous phenotype where multifactorial factors play a role in their development. These factors include, but are not limited to, genetic, age, insulin resistance (IR), chronic inflammation, dietary habits, physical activity, tobacco smoking, and alcohol abuse.[14,5,15–20] In fact, these culprit factors interact with each other and may potentiate the effect of each other during the course of

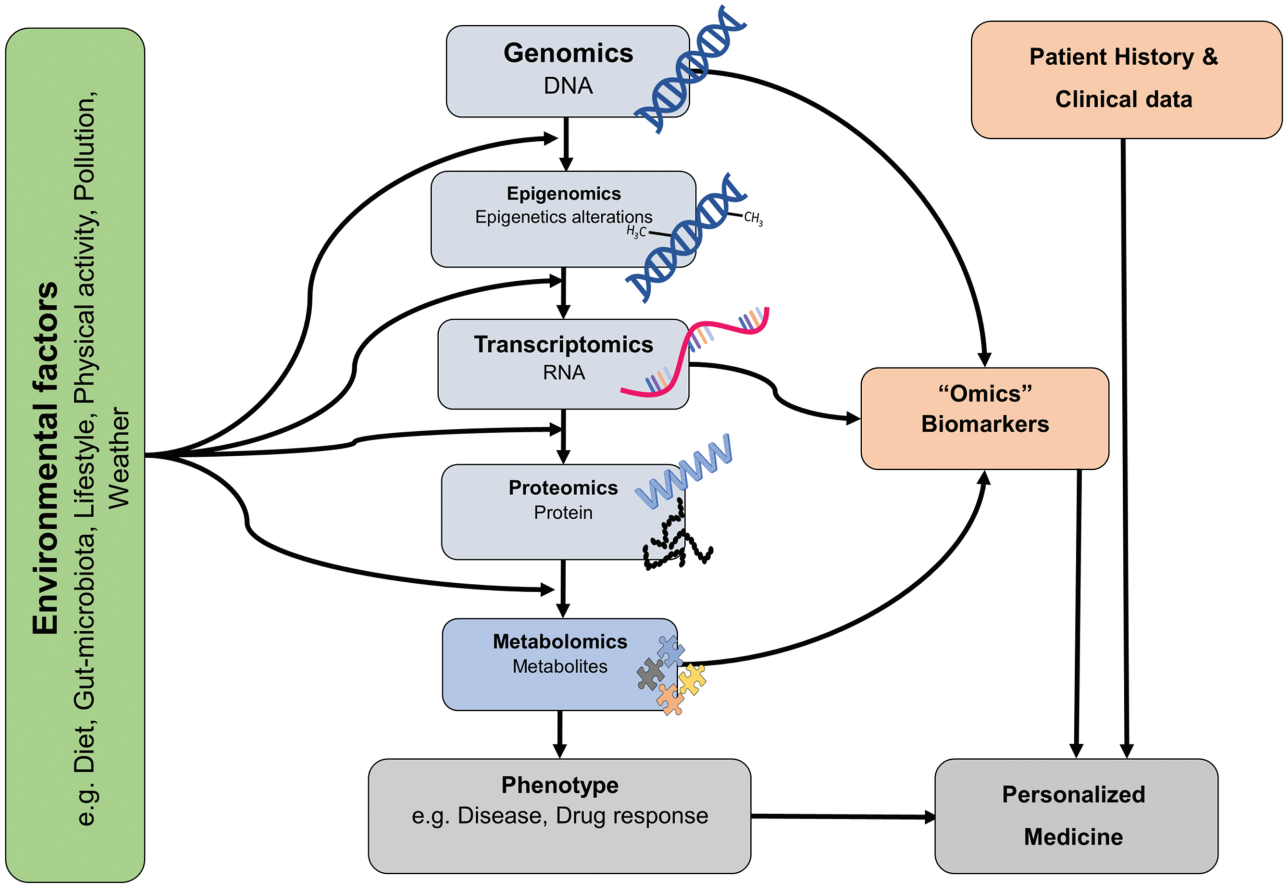

FIGURE 1 This figure displays the role of "Omics" biomarkers in predicting the phenotype and hence, personalizing therapy. Of all "Omics", metabolomics is the closest to the phenotype. Reprinted with permission from original source A. M. Amin, L. Sheau Chin, D. Azri Mohamed Noor, M. A. SK Abdul Kader, Y. Kah Hay and B. Ibrahim (2017). "The personalization of clopidogrel antiplatelet therapy: the role of integrative pharmacogenetics and pharmacometabolomics." *Cardiology Research and Practice***2017**: 17.

the disease's development and progression.[5,21] There have been many genetic variants including single nucleotide polymorphisms that were found to be associated with CMDs.[5,15,22] However, these genetic variants for most were not independent predictors and they were affected by interfering factors such as age, diet, lifestyle, sex, and environmental factors which may lead to augmentation or mitigation of their effect.[23,22] Therefore, genetic variants explain little of CMDs, however, often leading to a complexity in explaining a great portion of the pathogenesis of CMDs. It could be conceptualized that epigenetics alterations such as DNA methylation and histone modification may explain part of the CMDs complexity.[23] Unlike genetics which cannot be modified, epigenetic alterations are not constant, and it is possible to modify or reverse them by mitigating the implicated factors such as diet, lifestyle, and environmental changes.[23,24] With this understanding, identifying and targeting CMDs modifiable risk factors will have an auspicious impact on prevention and treatment.

Metabolomics is one of the "Omics" field that aims to identify metabolic traits associated with certain diseases, drug response, or dietary interventions.[25,26] This field comes in the "Omics" series after genomics, epigenomics, transcriptomics, and proteomics.[25,26] Metabolomics reflects variations in the preceding fields as well as changes in the metabolic pathways close to the phenotype, as shown in Figure 1.[25,26] In general, "Omics" series presents effective tools to personalize therapy where metabolomics closeness to the phenotype provides better insights and guide to the therapy.[27] Towards the identification of metabolic fingerprint (i.e., metabotype), metabolomic analysis is applied through the chemometric analysis of biosamples using spectroscopic techniques such as nuclear magnetic resonance (NMR) and mass spectroscopy (MS) coupled with gas chromatography (GC) GC-MS or liquid chromatography (LC) LC-MS to identify metabolic signatures associated with the phenotype.[25] The metabolomic approach has been applied to identify disease biomarkers, drug use biomarkers (i.e., pharmacometabolomics) such as drug response, drug toxicity, or drug exposure biomarkers, dietary intervention or nutritional therapy biomarkers (i.e., nutrimetabolomics), microbiome-related metabolites, and genetic variant biomarkers (i.e., metabolomics-informed genetics)..[27–30] Metabolic fingerprints, which are a group of metabolites associated with certain phenotypes (i.e., disease/drug/microbiome/genetic), usually shed light on the pathophysiologic/response factors associated with the phenotype, particularly if the metabolomic analysis is compiled with the pathway analysis.[28,31]

The metabolomic approach has been applied to identify metabolic traits of CMDs.[31–41] Moreover, it was also been applied in nutrimetabolomic and pharmacometabolomic investigations to identify CMDs dietary interventions and pharmacologic treatments metabotypes, respectively.[42–46] Despite the similarities and differences in the clinical features between each CMD and others, the metabolic fingerprints of different CMDs showed many similarities that may indicate potentially similar or linked pathogenesis.[27] In this narrative review, the literature on the metabolic signatures of CMDs and the shared traits between these signatures will be reviewed. A list of some common CMD metabolites available from the literature review and the metabolomic pathway analyses of these metabolites will be presented. Furthermore, therapeutic targets through dietary interventions and pharmacologic treatments that may interfere with the shared CMDs metabolic trait will be discussed. Towards that end, the literature used in this review was collected through searching in PubMed (MEDLINE). Common metabolites among CMDs metabotypes were summarized. Metabolomic pathway analyses to this shared metabotype were conducted using the metabolomic pathway analysis web-based software MetaboAnalyst 4.0.[47]

2 | INSULIN RESISTANCE DISORDERS

IR is the pathogenic phenotype of the reduced cellular response to insulin, the crucial glucose-metabolizing hormone which is secreted by the beta (β) cells in the pancreas.[48,49] IR leads to reduced glucose reuptake by the cells and eventually causes glucose intolerance and hyperglycemia.[48,49] As a compensatory mechanism, IR drives β cells to produce more insulin to maintain normoglycemia.[49,50] This increase of insulin to compensate IR (i.e., hyperinsulinemia) drives IR as well,[50,51] often leading to the occurrence of a vicious cycle of IR and hyperinsulinemia wherein both are results and drivers. IR and hyperinsulinemia are highly linked to the development of many diseases. Metabolic syndrome, obesity, type 2 diabetes mellitus (T2DM), and CVDs are just a few on the top of the list.[49,52–55] Many of IR-associated detrimental effects are due to hyperinsulinemia, being too much of a good thing (insulin). In fact, insulin has vital roles in the anabolic and the anticatabolic processes of the body, as shown in Figure 2A. Besides its role in stimulating glucose uptake by the cells, insulin stimulates glycogenesis, protein synthesis, lipogenesis, DNA replication, and fat storage.[56,57] On the other hand, insulin inhibits glycogenolysis, lipolysis, and gluconeogenesis.[56] Thus, insulin maintains metabolism and energy stores in our body; however, too much of a good thing may be harmful. This is the case of hyperinsulinemia.[58–63] Hyperinsulinemia is an independent risk factor for hypertension, atherosclerosis, dyslipidemia, endothelial dysfunction, CVDs, obesity, and T2DM.[58–63] Figure 2B depicts the relationship between hyperinsulinemia, IR, metabolic syndrome, obesity, dyslipidemia, atherosclerosis, T2DM, and CVDs. IR can be assessed by the estimation of the homeostatic model assessment of insulin resistance (HOMA-IR), which is a calculated value of (fasting glucose (mmol/ L) $\times$ fasting insulin (μU/mL) / 22.5).[64] As HOMA-IR estimate increases (more than 2), it indicates that the person is suffering from IR. Thus, HOMA-IR can be used as an indicator of IR and hyperinsulinemia.

There are three well-established IR disorders: metabolic syndrome, obesity, and T2DM. The three disorders may share many of the pathogenic pathways of insulin signaling, proinflammatory mediators, oxidative stress, mitochondrial dysfunction, and dysbiotic microbiota.[48,52–54,65–67] The literature on the metabolomic investigations of the three IR disorders has been growing substantially,[32,68,69–74] wherein the shared pathogenic pathways appeared clearly in their metabotypes.

2.1 | Metabolic syndrome metabotype

Metabolic syndrome is thought to be the most important root cause for CVDs and T2DM.[49] IR is the lineament feature of metabolic syndrome, a metabolic cluster which is highly associated with T2DM and CVDs.[75,76] The cluster of metabolic syndrome includes IR, glucose intolerance, hypertension, atherogenic dyslipidemia, and obesity, particularly intrabdominal obesity.[75] These manifestations clearly present the state of hyperinsulinemia in metabolic syndrome.[50,51] Besides the role of IR and hyperinsulinemia in the development of glucose intolerance, they have prothrombotic effect which increases the risk of CVDs in metabolic syndrome patients[77,78] (Figure 2B). Several studies were conducted to identify metabolic biomarkers of metabolic syndrome.[79–83] Metabolites which indicate glucose intolerance and perturbed glycolysis, gluconeogenesis, and fructose and mannose pathways are common metabolic biomarkers of metabolic syndrome.[74,84,80,85] Glycine, serine, and threonine (G-S-T) pathway metabolites such as serine, choline and threonine are indicative of IR and commonly perturbed in metabolic syndrome.[79–82] The branched chain amino acids (BCAAs); leucine, isoleucine, and valine which are indicators of IR, inflammation, and atherosclerosis, had been found associated with metabolic syndrome.[83,86] Acylcarnitines, which are associated with inflammation, IR, mitochondrial dysfunction and atherosclerosis, were metabolic biomarkers of metabolic syndrome as well.[87,79,88] In Table 1, metabolic syndrome biomarkers shared with other CMDs are tabulated. An enrichment overrepresentation (ORA) and pathway analyses of those biomarkers are presented in both Tables 2 and 3 as well as Figure 3.

2.2 | Obesity metabotype

Similar to metabolic syndrome, IR is a distinctive feature of obesity which associates obesity with other IR disorders.[52,53,48,54,89,90,38] Obesity is one of the crucial risk factors of T2DM and CVDs. Despite the multifactorial nature of obesity where genetic and nongenetic factors are implicated in its development, hyperinsulinemia and IR remain one of the most important pathogenic factors.[60,91] Indeed, hyperinsulinemia is one of the main driving factors of obesity, however often leading to IR.[91] This is due to the lipogenic effect of insulin

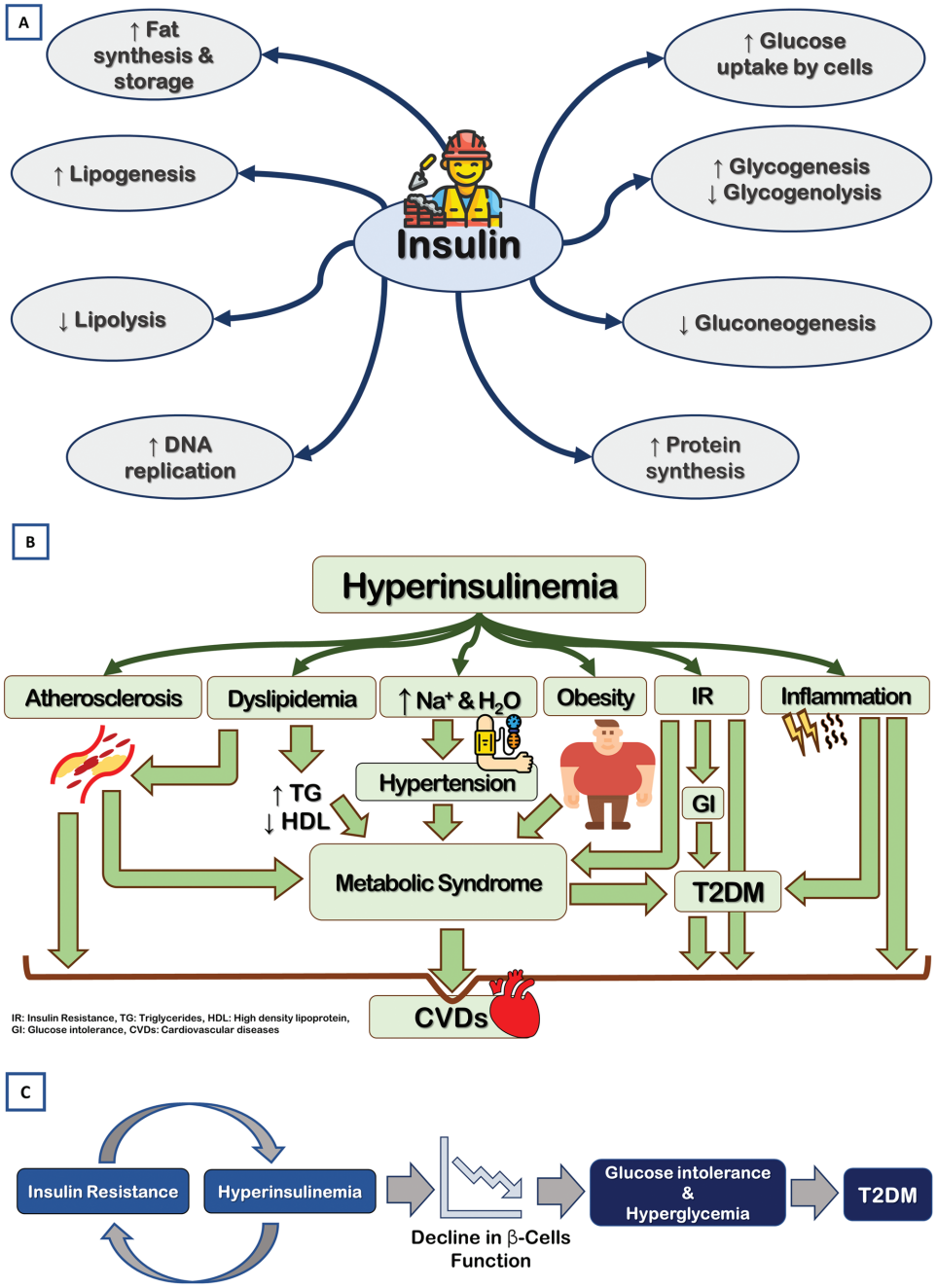

FIGURE 2 The role of insulin and the detrimental effect of the development of IR ↔ Hyperinsulinemia vicious cycle. (A) Anabolic and anticatabolic effects of insulin (↑ Stimulates, ↓ Inhibits). (B) The interaction between hyperinsulinemia, IR, inflammation and CMDs. (C) T2DM development is preceded by a vicious cycle of IR and hyperinsulinemia. Obesity, hypertension and Builder icons were from www.flaticon.com and they were made by Monkik, Smashicon and Wanicon, respectively

(i.e., stimulated lipogenesis) which leads to fat accumulation, which in turn increases IR.[52,53,56] Obesity metabolic biomarkers were investigated in several metabolomic studies. Many of these biomarkers are very similar to metabolic syndrome metabolomic biomarkers, and they indicate the presence of IR and inflammation.[38,35,71,92–94] Metabolic biomarkers of the G-S-T pathway such as betaine, serine, and threonine, as well as arginine–proline metabolism metabolites, such as citrulline, ornithine, arginine, and proline, are highly correlated with obesity.[38,35,71] In addition, metabolites of glycolysis and the gluconeogenesis pathway, such as glucose, lactate, and pyruvate as well as fructose and mannose pathway metabolites such as fructose and mannose, are implicated in obesity.[92,93,35,94] Moreover, dysbiotic gut microbiota metabolites such as trimethyl-amine-oxide (TMAO), choline, and hippurate are also linked to obesity.[35] Obesity metabolic biomarkers, which are shared with other IR disorders and CMDs, are listed in Table 1. Furthermore, an ORA and pathway analyses of those biomarkers are presented in both Tables 2 and 3 as well as Figure 3.

TABLE 1 Common metabolic biomarkers of CMDs (shared metabolic trait)

	Insulin resistance disorders			Cardiovascular diseases			
Metabolites	Metabolic syndrome elevated HOMA-IR / glucose intolerance	Obesity	T2DM	CVDs incidence/ CVDs- risk / Atherosclerosis	IHD /CAD / MI	HF / car-diomyopathy	Stroke/ carotid-atherosclerosis/ CI/ TIA
Glucose	74	159,93	68,32	127,160,161	31,135,160,162,121,154	163,164	124,125
Mannose	84	84,94,92,93	68,84	84,161	84,153,165	84	[161
Fructose	80,85	92,93	68,166,85	124	162,154	164	[124
BCAAs Leucine, isoleucine, valine	86,85,83	86,35,94	101,68,102,86,32,85,39	138,167,168,169	31,136,160,170,121	156,140,171,164	124,172
Acylcarnitines	87,79,88	139,87,94,93	139,68,87,32	122,173,167,168	173	41,140,141	122,172,174
Ceramides	87,83	87	87,147	87,123	175	176	145
L-lysine	79,82	35,71,79	32	169	31	156,171	3
L-proline	81,85	71	68,85	168	31	156,140	124
L-alanine	81,80	35,71,93	68,69,102	168	31,121	156,150,140	124
L-ornithine	81	71	68,69,70	177,168,169	31,160,177	41	174
L-histidine	81,88	94,71	69	178,169	31	156,41,140	[124
3-Methyl-histidine	179	180,179,71	68	169	31,121	164,181	172
L-arginine	79	35	70,102	70,177,168,169	177,121	156	174
L-serine	73,79	73,35	73,102	178,169	170	156	124
L-threonine	81,82	182	73,102,32	178,169	31,170	171	124
L-phenylalanine	79,85	35,94	68,85,39	168,169,36	31	156,41,171	124
Glutamine	79,80,85	79	69,85	168,169	31	140,164	124
L-lactic acid	79,80	35,94,79	68,32	127	135,183,162,154	156,150	124,125
Formate (Formic acid)	184,185	186	32,69	178	153,121	156	[172
Creatine	79,80	35	73,32,69	127	187,121	156	[125
Creatinine	79	35	68	160,124	31,160,153,165,121	150,156,41	124,125,188
Choline	80	35	32,104	126	31,127	156	125,188
Glutamate	80	35,94,93	68	168,169,124	160	140,171	124,125
Glycine	79,189	35,94,79	32	168,169,124	170	150,164	124,172
Taurine	79,80	35	69	190,169	190	150,171	125,172
Pyruvate	79	35	68	127,124	31,154	156,150	124,172
Hippurate	189,184	35,159,184	191	127	31	150	[172
TMAO	192	193,35	69,103	128,129,126	160,127,157	156,130	172
DMG	194	195	195,104	196,173,161	31,196,173,197	196,197	161
Phenylacetylglycine	198	159	69	199	31	150	199
Myoinositol	79	79	68	161	154,200	201	124
2-oxoglutarate(α-ketoglutarate)	202,203,83,88	203,35,92	69	204	205,204	201	125,33
3-hydroxybutyrate (β-hydroxybutyrate)	189,206	182	73,149	168,127,124	31,153,154	150,151	124
Acetoacetate	79	79,182	68,69,149	124	31	141	124
Acetate	79,189	35	32	178	153,165,121	156	207
Acetone	208,209	208,182	149	210	153	150,151	152

This table contains common metabolic biomarkers among several CMDs. Glucose intolerance as assessed by glucose challenge test.
Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance, T2DM, Type 2 diabetes mellites, CVDs, cardiovascular diseases, IHD, ischemic heart disease, CAD, Coronary artery disease, MI, Myocardial infarction, CI, cerebral ischemia, TIA, Transient Ischemic attack, Carotid-Athero, Carotid atherosclerosis, HF, Heart failure, BCAAs, Branched chain amino acids, DMG, dimethylglycine, TMAO, Trimethylamine oxide.[124,150,151,141,152,153,31,154].

TABLE 2 Enrichment ORA analysis of the shared CMDs metabotype

	Overrepresented metabolite sets[a]	Implicated metabolites[b]	Total [c]	Hits[d]	Raw *p*[d]	Holm *p*[f]	FDR[g]
1	Glycine and serine metabolism	Creatine; dimethylglycine; glycine; L-glutamic acid; L-alanine; L-threonine; L-serine; oxoglutaric acid; ornithine; pyruvic acid; L-arginine	59	11	3.27E-06	0.00032	0.00032
2	Urea cycle	L-glutamic acid; L-alanine; oxoglutaric acid; ornithine; pyruvic acid; L-arginine; L-glutamine	29	7	4.72E-05	0.00458	0.00182
3	Glucose–alanine cycle	D-glucose; L-glutamic acid; L-alanine; oxoglutaric acid; pyruvic acid	13	5	5.59E-05	0.00536	0.00182
4	Ammonia recycling	Glycine; L-glutamic acid; L-histidine; L-serine; oxoglutaric acid; pyruvic acid; L-glutamine	32	7	9.38E-05	0.00892	0.0023
5	Alanine metabolism	Glycine; L-glutamic acid; L-alanine; oxoglutaric acid; pyruvic acid	17	5	0.000241	0.0226	0.00472
6	Arginine and proline metabolism	Creatine; glycine; L-glutamic acid; L-proline; oxoglutaric acid; ornithine; L-Arginine	53	7	0.00242	0.225	0.0395
7	Amino sugar metabolism	Acetic acid; L-glutamic acid; pyruvic acid; L-glutamine; D-Fructose	33	5	0.00596	0.548	0.0688
8	Carnitine synthesis	L-Carnitine; glycine; L-lysine; oxoglutaric acid	22	4	0.0073	0.664	0.0688
9	Glutamate metabolism	Glycine; L-glutamic acid; L-alanine; oxoglutaric acid; pyruvic acid; L-glutamine	49	6	0.00752	0.677	0.0688
10	Methylhistidine metabolism	L-Histidine; 3-methylhistidine	4	2	0.00768	0.683	0.0688
11	Aspartate metabolism	Acetic acid; L-glutamic acid; oxoglutaric acid; L-arginine; L-glutamine	35	5	0.00772	0.683	0.0688

This metabolites enrichment analysis was generated by MetaboAnalyst 4.0 web-based program using the shared CMDs metabotype metabolites. (See Figure 3 for bar chart and dot plot visualization of this analysis.)
[a]Only pathway metabolite sets with $p < 0.05$ and FDR < 0.1 are shown in the table.
[b]Implicated metabolites from shared CMDs metabotype.
[c]Total number of metabolites in the metabolites set.
[d]Hits: number of metabolites from the shared CMDs metabotype involved in the metabolites set.
[e]Raw *p*: original *p* value calculated from the enrichment analysis.
[f]Holm *p*: adjusted raw *p* value by Holm-Bonferroni method.
[g]FDR: false discovery rate.

2.3 | T2DM metabotype

Similar to metabolic syndrome and obesity, T2DM is a complex disease where several genetic and nongenetic factors are involved in its development.[49,21] However, IR and hyperinsulinemia have been considered as the hallmark of T2DM pathophysiological development.[51,49,95] As aforementioned, IR usually leads to glucose intolerance and hyperglycemia,[48,49] which activate the compensatory mechanism of increasing insulin secretion by β cells to maintain normoglycemia.[49] Eventually, a vicious cycle of hyperinsulinemia and IR (hyperinsulinemia ↔ IR) develops leading to subsequent decline in β cells function (Figure 2C).[96–98] This will lead to glucose intolerance, followed by hyperglycemia and T2DM, as shown in Figure 2C. In fact, metabolic syndrome and obesity, two main IR disorders, represent an early sign of T2DM development. T2DM patients suffer many macrovascular and microvascular complications wherein CVDs are the most common.[99,55] In reality, the sustained state of the (IR ↔ hyperinsulinemia) vicious cycle preceding the development of hyperglycemia and the diagnosis of T2DM is one of the root causes of many T2DM complications such as atherogenic dyslipidemia, diabetic cardiomyopathy, CVDs, infectious diseases, and cancer[99,52,55,100,8,95,58–63] (Figure 2B).

Investigating T2DM metabolic biomarkers and related pathways has been applied extensively in the past decade. Researchers utilized metabolomic analyses of T2DM in plasma, serum, urine, and saliva.[101,68,102,86,32,85] Generally, metabolic biomarkers of glycolysis and gluconeogenesis pathway (i.e., glucose, lactate, pyruvate), fructose and mannose pathway (fructose, mannose), BCAAs pathway (i.e., leucine, isoleucine, valine), G-S-T pathway (i.e., serine, choline, dimethylglycine, glycine, threonine, creatine, pyruvate), ketone bodies pathway (i.e., 3-hydroxybutyrate, acetoacetate), aminoacyl-tRNA pathway (i.e., arginine; glutamine; glycine; serine; valine; alanine; lysine; isoleucine; leucine; threonine; proline; glutamate), acylcarnitines pathway as well as alanine–aspartate–glutamate pathway (i.e., alanine, glutamate, glutamine, pyruvate, 2-oxoglutarate) were among the most common T2DM metabolic biomarkers.[101,68,102,86,32,85,39] Furthermore, gut microbiota–derived metabolites, such as TMAO, choline, betaine, hippurate, dimethylglycine, and imidazole, are

TABLE 3 Metabolic pathways for the shared CMDs metabotype metabolites

	Metabolic Pathway[a]	Implicated metabolites[b]	Total[c]	Hits[d]	Raw *p*[d]	−log (*p*)[f]	Holm *p*[g]	FDR[h]	Impact[i]
1	Aminoacyl-tRNA biosynthesis	L-Histidine; L-phenylalanine; L-arginine; L-glutamine; glycine; L-serine; L-valine; L-alanine; L-lysine; L-isoleucine; L-leucine; L-threonine; L-proline; L-glutamate	48	14	5.64E-13	12.249	4.74E-11	4.74E-11	0.16667
2	Glyoxylate and dicarboxylate metabolism	L-Serine; glycine; L-glutamate; acetate; pyruvate; formate; L-glutamine	32	7	6.47E-06	5.1891	0.000537	0.000226	0.14815
3	**Glycine, serine and threonine metabolism**	**l-serine; choline; *N,N*-dimethylglycine; l-glycine; l-threonine; creatine; pyruvate**	**33**	**7**	**8.07E-06**	**5.0933**	**0.0007**	**0.0002**	**0.5354**
4	Arginine biosynthesis	L-Glutamate; L-arginine; L-ornithine; L-glutamine; 2-oxoglutarate	14	5	1.15E-05	4.9378	0.000935	0.000242	0.2538
5	Valine, leucine and isoleucine biosynthesis	L-Threonine; L-leucine; L-isoleucine; L-valine	8	4	2.01E-05	4.697	0.001607	0.000338	0
6	**Arginine and proline metabolism**	**l-Arginine; l-proline; l-glutamate; l-ornithine; pyruvate**	**38**	**6**	**0.00022**	**3.6482**	**0.0178**	**0.0031**	**0.3444**
7	**Glutamine and glutamate metabolism**	**l-Glutamate; l-glutamine; 2-oxoglutarate**	**6**	**3**	**0.0002588**	**3.5871**	**0.020183**	**0.003105**	**0.5**
8	Butanoate metabolism	(*R*)-3-Hydroxybutanoate; acetoacetate; L-glutamate; 2-oxoglutarate	15	4	0.0003461	3.4609	0.026646	0.003634	0.11111
9	**Alanine, aspartate and glutamate metabolism**	**l-Alanine; l-glutamate; l-glutamine; pyruvate; 2-oxoglutarate**	**28**	**5**	**0.00044**	**3.356**	**0.0335**	**0.0041**	**0.359**
10	**Synthesis and degradation of ketone bodies**	**3-Hydroxybutyrate; acetoacetate**	**5**	**2**	**0.0055882**	**2.2527**	**0.41912**	**0.046663**	**0.6**
11	Histidine metabolism	L-Glutamate; L-histidine; *N*(pi)-methyl-L-histidine	16	3	0.0061106	2.2139	0.45219	0.046663	0.22131
12	Nitrogen Metabolism	L-Glutamate; L-glutamine	6	2	0.008253	2.0834	0.60247	0.057771	0
13	Valine, leucine and isoleucine degradation	Acetoacetate; L-valine; L-isoleucine; L-leucine	40	4	0.014906	1.8266	1	0.091087	0
14	**Pyruvate Metabolism**	**Lactate; pyruvate; acetate**	**22**	**3**	**0.015181**	**1.8187**	**1**	**0.091087**	**0.35147**

This pathway analysis was generated by MetaboAnalyst 4.0 web-based software.
[a]Only metabolic pathways with $p < 0.05$ and FDR < 0.1 are shown in the table.
[b]Implicated metabolites from the shared CMDs metabotype.
[c]Total number of metabolites in the pathway.
[d]Hits: number of metabolites from the shared CMDs metabotype involved in the pathway.
[e]Raw *p*: original *p* value calculated from the pathway analysis.
[f]-log (*p*): negative log of (*p*) value.
[g]Holm *p*: adjusted raw *p* value by Holm-Bonferroni method.
[h]FDR: false discovery rate.
[i]Impact: impact of the pathway as calculated from the pathway topology analysis. Pathways in bold have the highest impact.

common T2DM metabolic biomarkers.[69,103,32,104,105] T2DM metabolic biomarkers, which are shared with other CMDs, are presented in Table 1. Enrichment ORA and pathway analyses of those biomarkers are listed and depicted in both Tables 2 and 3 as well as Figure 3, respectively.

3 | CARDIOVASCULAR DISEASES METABOTYPES

Cardiovascular diseases (CVDs) are conditions which affect the heart and blood vessels.[106] These include but is not limited to ischemic heart disease (IHD), CAD, HF, acute coronary syndrome (ACS),

and stroke. The most common pathogenic development in CVDs is atherosclerosis.[17] Atherosclerosis is an inflammatory process which leads to endothelial dysfunction and the formation of plaque in blood vessels.[17,107,108] If the plaque is ruptured, it may cause thrombosis leading to the development of several CVDs.[107] There are several factors that aggravate the atherosclerotic process such as IR, the presence of endothelial dysfunction, platelets dysfunction or reactivity, atherogenic dyslipidemia, low-grade inflammation, oxidative stress, and mitochondrial dysfunction.[109,16,17,110,18–20] Atherogenic dyslipidemia, mainly increased particle numbers of small low-density lipoprotein, apolipoprotein B (ApoB), and triglycerides, as well as the decreased level of high-density lipoprotein are significantly correlated with the development of CVDs.[111,112] This atherogenic dyslipidemia is highly derived by IR and hyperinsulinemia.[113–116] IR is associated with platelets and endothelial dysfunctions which increase the risk of developing CVDs in IR disorder patients.[77,78,62,59] Moreover, hyperinsulinemia increases the risk of developing CVDs.[117] In fact, elevated blood glucose is associated with platelets hyperactivity and increased intima-media thickness of common carotid arteries.[118,119] Thus, this detrimental effect is highly manifested in individuals suffering from prediabetes and T2DM.[119] However, nondiabetic CVDs patients are not shielded from this harmful effect if they endure from IR.[99] Platelets dysfunction, higher platelets reactivity, and resistance to antiplatelets therapy are highly derived by IR, hyperinsulinemia, and insulin therapy.[109,21,43,120] As such, IR is one of the main predictors of cardiac events.[55,99]

There have been several metabolomic studies conducted to discover metabolomic biomarkers of CVDs and their risk.[27,31,36] Perturbations in the metabolic pathways of aminoacyl-tRNA biosynthesis, urea cycle metabolism, arginine and proline metabolism, ketone bodies, glycolysis or gluconeogenesis, G-S-T metabolism, BCAAs biosynthesis and degradation, alanine–aspartate–glutamate metabolism, acylcarnitines, and galactose metabolism had been commonly described in CVDs metabolomic studies. [31,121–125,36] This indicates that there are common metabolites associated with CVDs such as glucose, BCAAs, lactic acid, galactose, acylcarnitines, ceramides, ketone bodies, and other amino acids. Furthermore, there are also disturbed gut microbiota–derived metabolites associated with CVDs such as TMAO, choline, and betaine.[126,31,127–130]

4 | THE SHARED CMDs METABOLIC TRAIT AND PATHWAY ANALYSES

As discussed in Sections 2 and 3 of this review, CMDs have shared pathogenic pathways, which include but are not limited to IR, insulin signaling, low-grade inflammation, oxidative stress, and dysbiotic gut microbiota.[89,21,131] Upon review of the literature, this shared pathogenicity is highly reflected on the metabolome. In Table 1, around 40 common CMDs metabolomic biomarkers are presented with reference to their literature. Since metabolomic has the advantage of mirroring condition's pathogenic pathways, analyses of the metabolic biomarkers against pathways platforms, such as metabolites sets, and metabolic pathways usually give in-depth understanding of condition's related perturbations. Towards having better conceptualization of the shared metabotype, an ORA of metabolites' sets and pathway analyses for the list of the metabolites in the CMDs-shared metabotype (Table 1) were performed using MetaboAnalyst 4.0 web-based free software,[47] as shown in Tables 2 and 3 and Figure 3. The enrichment of ORA for the metabolites in the CMDs-shared metabotype against the metabolic pathway-associated-metabolite sets library showed that glycine and serine metabolism had the highest significance and the lowest false discovery rate (FDR). Other significant metabolite' sets (11 metabolites' sets) are presented in Table 2 (p value < 0.05 and FDR < 0.1). Figures 3A and 3B depict bar chart and dot plot views of the enrichment ORA, respectively. The pathway analysis of the metabolites in the CMDs-shared metabotype revealed that G-S-T metabolism, arginine, and proline metabolism, glutamine and glutamate metabolism, alanine–aspartate–glutamate metabolism, synthesis and degradation of ketone bodies, and pyruvate metabolism pathways had the highest impact among 14 significantly implicated pathways in the shared CMDs metabotype (p value < 0.05 and FDR < 0.1). Table 3 demonstrates 14 significant pathways that had the lowest FDR. Figure 3C illustrates the significance and the impact of the pathways. Figures 3D and 3E show the pathways of G-S-T metabolism and synthesis and degradation of ketone bodies, respectively (i.e., the most impactful pathways). Figure 3F depicts the aminoacyl-tRNA biosynthesis pathway (i.e., the most significant pathway).

The shared CMD metabolites and the pathway analyses indicate that IR disorders and CVDs share many metabolic pathways. In fact, many of the identified perturbed metabolic pathways such as aminoacyl-tRNA biosynthesis, G-S-T, ketone bodies, pyruvate, BCAAs (leucine, isoleucine, valine), histidine metabolism, as well as arginine–proline metabolism pathways were previously reported in the metabotypes of each CMD.[68,31,74,32,69,35,34,132,121] Changes in metabolites levels, such as D-glucose, fructose, mannose, lactic acid, and galactose as well as changes in amino acids had been described in both IR disorders[68,133,32,69,134,71,101,121] and CVDs.[121,135,36] Other examples of the CMDs-shared metabolic biomarkers are the BCAAs, acylcarnitines, ceramides, and ketones bodies. BCAAs; L-leucine, L-isoleucine, and L-valine are well-established biomarkers of IR disorders, HOMA-IR, β cells functions, as well as CVDs risk.[68,136,137,86,138,121,39] In a study to identify plasma metabotypes of CAD, T2DM, and CAD-T2DM as discriminated from healthy control subjects, perturbations in glucose, BCAAs, and other amino acids were associated with the three groups T2DM, CAD, and CAD-T2DM.[121] Acylcarnitines have been found to be associated with CVDs including stroke incidences, as well as IR disorders.[87,79,139,68,32,122,41,140,141] Acylcarnitines are proinflammatory and instigate oxidative stress, as well as mitochondrial dysfunction[142,143] which highlight the implicated role of acylcarnitines in CMDs development.[122,142,143,87,144] Similarly, ceramides which are metabolic biomarkers of CVDs incidences, stroke, and T2DM[123,87,145] are indicative of IR, inflammation, and mitochondrial dysfunction.[123,146–148,87] Ketone body metabolites such as acetone, acetoacetic acid, and 3-hydroxybutyrate (β-hydroxybutyrate) are metabolic biomarkers of CMDs.[149,68,124,150,151,141,152,153,31,154]

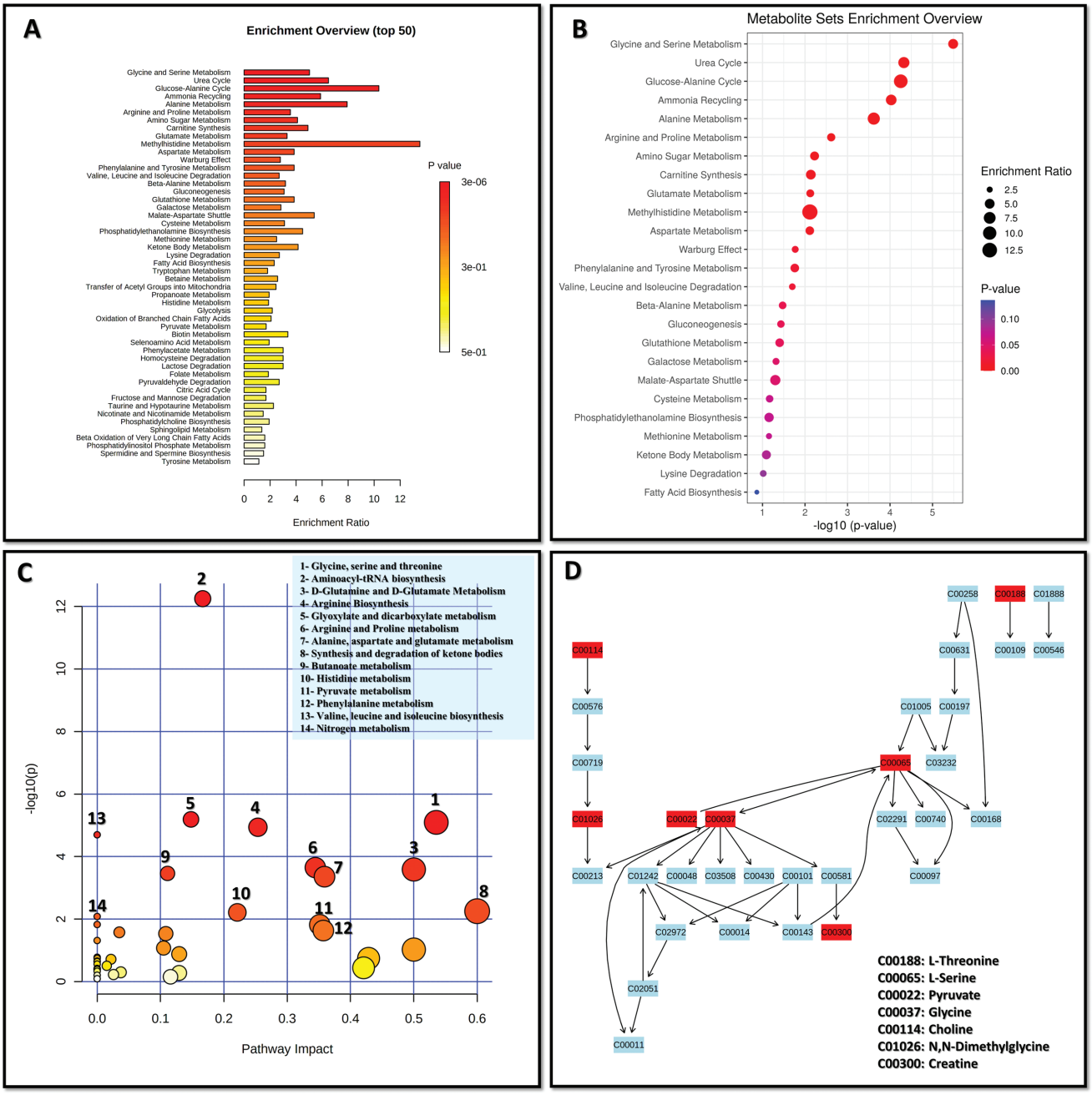

FIGURE 3 The results of pathway analysis and enrichment analysis of the shared CMDs metabotype as generated by MetaboAnalyst 4.0 web-based software. (A) Bar chart view of the over representation enrichment overview based on Small Molecule Pathway Database (SMPDB). Pathway metabolites sets are sorted based on fold enrichment and *p* value. Glycine and serine metabolism, urea cycle, and glucose-alanine cycle had the most significance. (B) Dot plot view of the overrepresentation enrichment overview based on SMPDB. Pathway metabolites sets are sorted based on fold enrichment and *p* value. Glycine and serine metabolism, urea cycle, and glucose-alanine cycle had the most significance. (C) Pathway analysis of the shared CMDs metabotype metabolites based on *Kyoto Encyclopaedia of Genes and Genomes* (KEGG) showed that synthesis and degradation of ketone bodies followed by glycine, serine, and threonine had the highest impact while aminoacyl-tRNA biosynthesis followed by glyoxylate and dicarboxylate metabolism had the highest significance. Refer to Table 3 for further details on the *p* value, FDR value, and the impact of each pathway. (D) Glycine, serine, and threonine pathway. (E) Ketone bodies pathway. (F) Aminoacyl-tRNA biosynthesis. Cxxxxx numbers are identifiers for metabolites mapped in a KEGG pathway. Red blocks indicate CMDs metabotype metabolites present in the pathway, and blue blocks are other metabolites present in the pathway

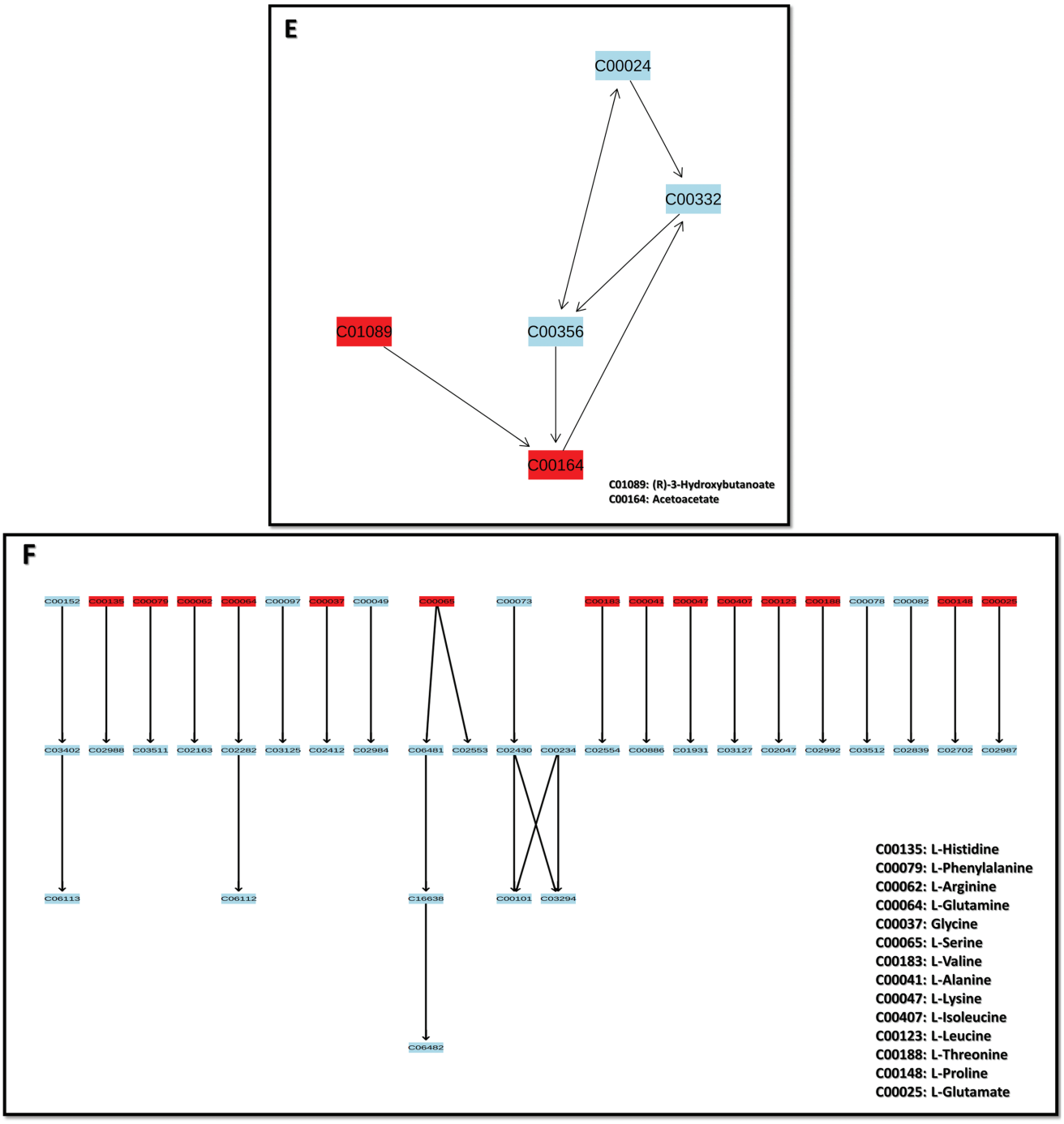

FIGURE 3 Continued

β-Hydroxybutyrate may elevate in CVDs as a compensatory mechanism, which may have a potential cardioprotective role.[155] Other examples of CMDs metabolomic biomarkers include arginine, ornithine, proline, pyruvate, and glutamate, the metabolites of the arginine, and proline metabolism pathway.[156,79,31,85,71,124] Indeed, the increased activity of arginase enzyme causes the accumulation of proline and ornithine in patients enduring from IR disorders.[70] As such, this mitigates the formation of nitric oxide (NO) leading to elevated reactive oxygen species, endothelial dysfunction, and macrovascular complications. Dysbiotic gut microbiota–derived metabolites such as TMAO, choline, betaine, and hippurate that are known to be correlated with atherosclerosis, high platelets reactivity ,and antiplatelet resistance are also common among CMDs.[120,129,128] In fact, TMAO was found to be associated with IR and T2DM incidences.[103] Furthermore, TMAO has been found to be associated with major cardiovascular events and mortality risk in T2DM.[157] Imidazole propionate, which is also gut microbiota–derived metabolite, has been found to be elevated in T2DM patients and is associated with the impairment

of insulin signaling.[105] This indicates that gut microbiota is highly implicated in IR disorder pathogenesis. These common metabolic biomarkers and metabolic pathways between CVDs and IR disorders explain to a large extent the pathogenic interrelation between CVDs and IR disorders.[158] In a proposed diseasewise classification for CAD metabotypes (plasma and urine), the metabolic signatures of IR, T2DM, dyslipidemia, mitochondrial dysfunction, atherosclerosis, cardiomyopathy, HF, dysbiotic gut microbiota, and low-grade inflammation were highly represented in CAD metabotypes.[31] Furthermore, metabolic phenotyping and diseasewise classification of clopidogrel response among the same CAD population indicated similar CMDs multifactorial.[120,43] The diseasewise classification of clopidogrel high on treatment platelets reactivity metabotypes revealed that the metabolic traits of IR, T2DM, metabolic syndrome, obesity, and dysbiotic microbiota are highly represented.[120,43] As such, one can contemplate that CVDs metabotypes not only share metabolic signatures with other IR disorders metabotypes but also this shared signature plays a substantial role in patients' response to treatment.

5 | CMDs THERAPEUTIC-METABOLOMIC: CURRENT STATE AND FUTURE PERSPECTIVES

From the shared CMDs metabolic trait, genuine CMDs therapeutic targets are likely conceivable. Reducing IR, inflammation, and mitochondrial dysfunction, as well as maintaining healthy gut microbiota and weight reduction strategies are all sensible therapeutic targets for CMDs. This can be achieved through lifestyle interventions and pharmacologic treatment approaches. Lifestyle modifications such as dietary interventions, caloric restriction, exercise, and intermittent fasting are effective approaches that work on the implicated pathogenetic pathways.[12,211–215,64,216–219] Pharmacological treatment such as DM and CVDs drugs may work also on the same pathways. There are nutrimetabolomic and pharmacometabolomic studies investigating the effect of dietary interventions and pharmacological management on CMDs, respectively. In the following subsections, the two CMD therapeutics approaches along with some metabolomic literature on them will be discussed.

5.1 | Dietary interventions in CMDs

Since dietary habit is a significant driving factor in the development of IR disorders and CVDs, dietary interventions play a vital role in the prevention and the management of these conditions. One of the well-established dietary interventions for the prevention and management of CMDs is the Mediterranean diet which is known to be rich in nuts, extra virgin olive oil, fatty fish, seeds, vegetables, fruits, fibers, and resistant starch.[220,218,219,122,138,221] The American College of Cardiology/American Heart Association Guidelines on the Primary Prevention of Cardiovascular Disease recommended the Mediterranean diet supplemented with extra-virgin oil or nuts as a lifestyle intervention for CVDs prevention.[222] This diet had promising results in the management of obesity and metabolic syndrome, as well as in reducing the incidences of both T2DM and CVDs.[220,218,219,122,138] In addition, the Mediterranean diet with restricted carbohydrate and enriched virgin olive oil showed favorable results compared to the low-fat diet in reducing T2DM and CVDs incidences among individuals with a high risk to develop CMDs.[220] In the Prospective Urban Rural Epidemiology (PURE) study, it was found that a high consumption of nuts was associated with reduced CVDs mortality.[223] The effectiveness of the Mediterranean diet (generally) and the Mediterranean diet-food (specifically) in CMDs treatment has been investigated in several metabolomic studies. For instance, the Prevención con Dieta Mediterránea (PREDIMED) trial showed that the Mediterranean diet interfered with BCAA, acylcarnitines, and ceramides, the well-established metabolic biomarkers of IR disorders, and CVDs.[122,138,123] In fact, reducing dietary intake of BCAA may increase insulin sensitivity and hence reduces IR.[45] Mediterranean diet food such as cocoa reduced acylcarnitines in individuals with increased CVD risk in a LC-MS metabolomic study.[224] Thus, dietary intervention with dark chocolate, cocoa, and almonds improved lipid profile in overweight and obese subjects.[225] Pistachios and almonds showed a positive gut-modulation role by changing dysbiotic microbiota–associated metabolites such as TMAO, 4-cresol, and hippurate levels in prediabetes and metabolic syndrome.[44,42] Since TMAO was associated with cardiovascular events and mortality risk in T2DM,[157] the well-established cardioprotective role of pistachios is recognizable.[226,221] Eating meals enriched with blueberries was associated with significant reduction in methylamines, acetoacetate, acetone, and succinate in obese subjects suffering from metabolic syndrome, suggesting a modulatory effect of blueberries on gut microbiota.[208] Noteworthily, blueberries consumption has anti-inflammatory and antioxidative stress effects which tackle crucial pathogenic pathways in CMDs. Four weeks of dietary intervention which includes fibers and resistant starch food led to the elevation in short chain fatty acids (SCFA) compounds such as acetate and butyrate through a modulatory effect on gut microbiota.[46] In fact, SCFAs have a regulatory effect on insulin sensitivity leading to improvement in body weight, glucose homeostasis, and IR.[227,228] Consumption of nontoxic doses of 4-cresol, which is a metabolite present in smoked foods, dairy products, asparagus, coffee and is produced from the colonic fermentation of tyrosine and phenylalanine amino acids, was found to improve glycemic control, triglycerides, and β-cells proliferation.[229]

Similar to the Mediterranean diet and probably more effective in IR disorders is the low carbohydrate healthy fat (LCHF) diet (i.e., ketogenic diet), which is one of the recommended nutritional therapies for T2DM by several consensus reports and position statements.[230–233] The LCHF diet focuses on restricting carbohydrates, mainly the high glycemic index and glycemic load food, while utilizing healthy fat as the main source of energy and maintaining moderate amounts of protein.[213] The LCHF dietary intervention helped to achieve normoglycemia and reverse prediabetes which is an early prevention of T2DM.[234] This dietary approach was found to reduce HOMA-IR, weight, atherogenic dyslipidemia, HbA1c, and DM medications in the three main IR disorders: metabolic syndrome, obesity, and

T2DM.[211–213,235–239] Compared to the low-fat diet, the LCHF was more effective in the treatment of metabolic syndrome.[240] Since eating high carbohydrate food, particularly those of high glycemic type (high glycemic load and high glycemic index) was associated with higher CVDs risk and mortality,[113,241–243] the LCHF showed high effectiveness in the prevention and management of CVDs.[212,236,237] It is plausible to understand this effectiveness with the LCHF role in reducing the detrimental effect of IR and hyperinsulinemia which may lead to CVDs development (Figure 2B). Indeed, consumption of high glycemic food causes spikes of glucose and insulin secretion (postconsumption) which may lead to hyperinsulinemia and IR.[91] In fact, the LCHF reduced systolic and diastolic blood pressure as well as the use of antihypertension medications.[212,236,237] It also reduced risk factors of CVDs, such as atherogenic dyslipidemia as well as the inflammatory biomarkers, C-reactive protein, and white blood cells.[212,236] Another cardioprotective role of the LCHF is that it increases the level of circulating ketone body: β-hydroxybutyrate.[244,245] β-Hydroxybutyrate has a cardioprotective role through its vasodilatory effect and the reduction of oxidative stress in the cardiomyocytes.[155,246–248] Considering the aforementioned role of the LCHF diet, one can contemplate the findings of the PURE study, which was conducted in 18 countries from five continents and indicated that people who consumed high carbohydrates, particularly from refined resources, had higher risks of total mortality.[249] However, dairy products were associated with reduced CVDs mortality. Unlike the Mediterranean diet, the metabolomic data on the role of LCHF diet in CMDs treatment are limited. The LCHF effect on the metabolome has been investigated in cancer and epilepsy as well as in inflammatory diseases such as psoriasis[250–252]; however, to the best of this author's knowledge, the LCHF-metabolomic study has not yet been applied to CMDs. Some of the LCHF metabolomic studies investigating non-CMDs diseases indicated a regulatory effect of the diet on some metabolites implicated in the shared metabotype of CMDs. For instance, the LCHF diet significantly reduced ceramides in pancreatic cancer patients postpancreatectomy which are metabolic biomarkers of CMDs as well.[250] Another example of this regulatory effect had been seen with psoriasis disease regression in psoriasis patients following the LCHF diet as a nutritional anti-inflammatory therapy.[251] The LCHF diet significantly reduced lactic acid, isoleucine, leucine, and alanine in psoriasis patients treated with this dietary approach. Whether the LCHF diet may yield similar or more robust effects on the shared CMD metabotypes warrants research investigation, particularly that LCHF was clinically effective in the management of CMDs.

5.2 | Pharmacological treatment for CMDs

In addition to dietary interventions, pharmacologic treatments can play a vital role in targeting the metabolic pathways implicated in CMDs metabolic trait. This was manifested by pharmacometabolomic studies investigating T2DM and CVDs medications. For instance, metformin is an insulin sensitizer drug, which is considered the first line for pharmacologic treatment of T2DM.[253,254] Beyond its role in the treatment of IR, glucose intolerance, and T2DM, metformin can restrain oxidative stress, mitochondrial dysfunction, and inflammation.[255–257] This pleiotropic effect has increased the interest in the role of metformin for the treatment of several other diseases such as polycystic ovary syndrome, CVDs, cancers, Alzheimer's disease, and infections.[258–262,255] Such diseases have shared pathogenic pathways such as IR, oxidative stress, mitochondrial dysfunction, and low-grade inflammation which may, in part, explain the metformin role in their treatment.[258,257] In the context of CMDs, besides its role in nullifying IR, a substantial culprit factor in IR disorders and CVDs,[55] metformin reduces platelets reactivity and atherosclerosis.[255,263,258] Therefore, it has cardioprotective role in individuals suffering from T2DM and metabolic syndrome.[264,260] In a rat model of T2DM, the metabolomic analysis of urine samples showed that metformin modulated the activity of gut microbiota.[265] Moreover, metformin led to a reduction of 2-oxoglutarate, one of the candidate metabolic biomarkers of CMDs in the current review.[265] It is noteworthy to mention that the metabolomic study indicated that plasma imidazole propionate could be a biomarker of metformin resistance.[266] Imidazole propionate, a gut-derived metabolite that has been found elevated in T2DM, interferes with the effectiveness of metformin leading to poor glycemic control.[266] Another example of pharmacological treatment with a potential effect on the metabolic trait of CMDs is the sodium–glucose cotransporter inhibitors (SGLT2i) such as dapagliflozin, canagliflozin, and empagliflozin. SGLT2i are T2DM drugs, which achieve their hypoglycemic effect by increasing the excretion of glucose in urine. SGLT2i drugs have a CMDs beneficiary effect by reducing BCAAs,[267] which are candidate metabolic biomarkers of CMDs as well (Table 1). Furthermore, SGLT2i drugs have a cardioprotective role, particularly in HF prevention and treatment.[267] This role, in some part, may be attributed to the increased level of the ketone body β-hydroxybutyrate, a perturbed metabolic biomarker for CMDs (Table 1). As mentioned earlier, β-hydroxybutyrate is an alternative fuel which has a cardioprotective effect by increasing vasodilatation and counteracting oxidative stress.[155,246,247] However, a drawback of SGLT2i is that they have high risk of euglycemic ketoacidosis side effect due to the potentially poorly controlled β-hydroxybutyrate levels in individuals suffering from IR.[268] Therefore, in this context, it is worthy to mention that combining SGLT2 inhibitors with the LCHF dietary intervention is not recommended since this combination may increase the risk of developing euglycemic ketoacidosis.[269]

Similar to T2DM medications pharmacometabolomic studies, some of the CVDs medications have potential role in tackling some of the CMDs implicated metabolic pathways. For instance, antihypertensive drugs such as bisoprolol, amlodipine, and losartan were found to reduce acylcarnitines in plasma.[270] Acylcarnitines are indicative of IR, inflammation, and mitochondrial dysfunction in CMDs.[122,142,143,87] In fact, these drugs have potential anti-inflammatory action beyond their antihypertensive properties.[271–273] Whether a follow-up of acylcarnitines levels will help to indicate responsiveness to the anti-inflammatory effect of these pharmacological treatments, merits further investigations.

6 | CONCLUSION

CMDs develop over a long course of time, and hence by manipulating some of the contributing risk factors they can be prevented. Early prevention and treatment of CMDs will reduce the global NCDs mortality and improve quality of life. This will have thriving impacts on public health and economics. It will also improve the outcome and reduce mortality and morbidity in any future pandemic. CMDs have shared metabolic traits, which highlight several contributing risk factors and implicated metabolic pathways such as IR, mitochondrial dysfunction, oxidative stress, low-grade inflammation, and dysbiotic gut microbiota. These pathways can be targeted with nutritional and pharmacological therapeutic interventions. However, limited metabolomic literature is available on CMDs therapeutics. CMDs metabolic signature can be used for early prediction of individuals at higher risk of CMDs development, as well as the follow-up of treatment interventions. However, further investigations are warranted. Based on the shared metabolic pathways, one can suggest that nutritional therapy such as the Mediterranean and the LCHF dietary interventions can potentially target some of the implicated metabolic pathways in CMDs. These dietary interventions may offer early lifestyle management for individuals at high risk for developing CMDs. Although these approaches have been recognized by several guiding consensus, their implementation is still limited in clinical practice. Moreover, some pharmacologic treatments can target some of the shared CMDs metabolic pathways and hence can be added to a well-optimized CMDs prevention and treatment protocol. This protocol, meriting further investigation and validation, can be implemented with the collaborative efforts of healthcare professionals and public health authorities. Although this review shed light on the shared CMDs metabolic pathways, it suffers limitations. The subjective nature of the narrative review which sometimes affects the conclusions drawn. Therefore, future systematic reviews of CMDs metabotype may robustize the conclusions. There are scarce metabolomic data (in general) on the dietary interventions in CMDs, particularly on the LCHF diet. More studies are required to investigate the CMDs metabotype and the effect of therapeutic strategies on them.

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DATA SHARING

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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ORIGINAL ARTICLE

Educational interventions to improve maternal-foetal outcomes in women with gestational diabetes

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Abstract

Aims: To evaluate improvement in gestational diabetes (GDM) outcomes for mothers and their offspring induced by education provided to the healthcare team (HCTM) and women with GDM, plus coordination between primary care units (PCU) and highly complex maternity (HCM) facilities.

Methods: Pregnant women with GDM completing control visits from first appointment until delivery were recruited in participating PCU-HCM, in the cities of Corrientes and Buenos Aires; 263 women recruited from 2017 to mid-2018 were assigned to the control group (CG), and 432 women recruited from mid-2018 to 2019 to the intervention group (IG). The CG received standardized care/routine management and follow-up, including basic information on blood glucose monitoring and insulin injection when necessary, whereas the IG received an educational program targeting HCTM and women with GDM. These courses included standards of diagnosis, prevention and treatment of GDM, plus systematic registry of clinical and metabolic indicators (fasting blood glucose, serum cholesterol and triglyceride). Data on obstetric history, preeclampsia, gestation-induced hypertension, delivery method and newborn's body weight were also recorded

Results: Women in the IG showed significantly ($P \leq 0.05$) lower BMI and weight gain during gestation, a trend towards lower triglyceride and caesarean sections and a significant increase in postnatal attendance for metabolic assessment. Their newborns showed significantly lower body weight and a trend towards fewer macrosomia.

Conclusions: These data suggest that our educational intervention plus management changes induced a favourable impact on GDM outcomes for both mothers and offspring.

KEYWORDS
education, gestational diabetes, newborn weight, postnatal assessment, pregnancy weight gain

1 | INTRODUCTION

The prevalence of type 2 diabetes (T2D) grows ceaselessly worldwide, mainly due to a combination of a population epidemiologic transition towards aging, a more sedentary lifestyle, and a growingly earlier age of onset.[1] Although this phenomenon occurs globally, it mainly affects developing countries.[2] Simultaneously, the prevalence of gestational diabetes (GDM), one of the most common complications of pregnancy, has increased by over 30% in recent decades in several countries,[3,4] thereby conforming an emerging worldwide epidemic.[5]

Globally, about 17% of pregnancies are affected by GDM, but its incidence ranges from 1% to over 25% depending on diagnostic criteria and maternal risk.[6–11] Its prevalence in South and Central America is estimated at 11.2% (CI, 7.1-16.6%)[9] with comparable statistics reported for Argentina.[12]

GDM is associated with a higher risk of adverse health outcomes during pregnancy and delivery for both mothers and babies. Women with GDM have a higher risk of developing complications during pregnancy such as preeclampsia, instrumental deliveries, caesarean section, postnatal DM and obesity, whereas their newborns have a higher risk of developing short-term adverse events (macrosomia, neonatal hypoglycaemia, respiratory distress syndrome and neonatal cardiac dysfunction), as well as long-term metabolic dysfunctions.[13,14]

This negative impact on the mother and offspring can be significantly reduced by early diagnosis and adequate treatment combining the adoption of a healthy lifestyle and, when needed, medication.[15,16]

Despite this heavy clinical impact, few studies have investigated its economic burden: in the United States, the estimated cost of pregnancy with GDM was double that of normal pregnancy (a difference of U$ 7803).[17] In China, considering only the cost during the last gestational trimester, the estimated difference in cost between a pregnancy with and without GDM was U$ 1008 (+95%); in 2015, its total burden was U$ 2.92 billion (¥19.36 billion).[18] Studies in different European countries reported an increase ranging from 20% to 130%, respectively.[19–21] In Mexico, the care cost of a pregnancy with GDM was 56.1% higher than that of a pregnancy without GDM.[22] Such large differences could be attributed to local healthcare systems, demography and ethnic characteristics, as well as the application of different methodologies. All of them, however, highlighted the considerable economic burden and cost differences between pregnancies with and without GDM.

Although it has not been clearly shown, we assume that the economic burden in Argentina is similar. Therefore, in an attempt to decrease this burden upon women with GDM and its economic impact on the healthcare system, we have developed and implemented (a) an educational approach that targets members of the healthcare team (HCTM) at the primary/high complex care level and women with GDM and (b) close contact/interaction between primary care level and maternity hospitals to ensure that every woman with GDM is seen at the appropriate high complexity level. Our study aims to assess the impact of this educational approach and management changes on outcomes for mothers and their offspring.

2 | MATERIALS AND METHODS

Pregnant women with GDM consulting for medical care were sequentially recruited between 2017 and 2019 in primary healthcare centres in combination with participating high complexity maternity (HCM) facilities. Participating HCM were one in the J. R. Vidal Hospital (Corrientes Province) and another in the Argerich Hospital (Buenos Aires City). Every pregnant woman diagnosed with GDM was immediately referred to the HCM.

During this 2-year period, we recruited women with GDM at weeks 28-30 of pregnancy in a chronological sequential order. GDM patients were diagnosed according to Latin American Diabetes Association (ALAD), which is based on glycaemia values either at fasting or after the universal oral glucose tolerance test performed on weeks 24-28 of pregnancy.[23] The recruited women attended follow-up visits from the first clinical appointment and until they delivered the baby.

As exclusion criteria, we excluded women under 18 years of age due to our law regarding underage patients,[24] those with pre-GDM, those who have previous history of serious obstetric complications as well as those who declined to sign the informed consent.

All women with GDM who met the abovementioned conditions and were recruited – in a sequential order – were as follows: Those recruited from 2017 to mid-2018 were assigned to the control group (CG), whereas those recruited from mid-2018 to 2019 were assigned to the intervention group (IG). Applying this procedure, we recruited 263 and 432 women with GDM for the control and intervention groups, respectively.

The women included in the CG received standardized care/routine management and follow-up, including basic information on blood glucose monitoring and insulin injection when necessary.

For the IG, we developed and implemented an educational programme, named EduGest, targeting different members of the HCTM and women with GDM, especially adapted to each of these audiences. Detailed descriptions of the later program have been already reported.[25] Briefly, starting at enrolment, we gave weekly small-group interactive theoretical-practical courses that included basic physiological concepts of the gestation process, foetal growth, normal vaginal delivery and caesarean section, healthy maternal meal plan, physical activities, breast-feeding and explanations of a model for insulin-self-injection practices, blood glucose self-monitoring (SMBG) and data interpretation. Participants were also given a manual summarizing all these contents. These courses were delivered by pre-trained team members – mainly nurses. It also provided educational material (Power Point material and some models such as a perineum and vaginal canal to simulate childbirth) to ensure their effectiveness.

The education program for the IG also includes physicians and nurses who attended a separate, intensive course with specific contents such as standards of diagnosis and prevention and treatment of the disease. Evaluations of their knowledge were taken before and after these courses using multiple-choice questionnaires. They also provide training to enable healthcare professionals to update the QualiDiabGest, NutriQuidGest and WHO-5 registries. The QualiDiabGest

includes clinical-metabolic and gestational events corresponding to the mother and the foetus/newborn.[25] The NutriQuidGest[26] analyses the patient's self-reported food intake and calculates the essential components and nutritional value. The WHO-5 evaluates the patient's well-being and tendency to depression.[27,28] Data were evaluated to assess the impact of the educational programme on GDM outcomes. With all these data, we addressed the evaluation of the impact of the educational program on GDM outcomes.

In both CG and IG groups, each woman's clinical and metabolic data were registered using the QualiGest form, designed and validated especially for the EduGest study.[25] This form includes personal data and obstetric history, body mass index (BMI), blood pressure, cardiovascular risk factors, fasting blood glucose (FBG), serum total cholesterol and triglycerides. It also includes data on the woman's obstetric history, characteristics of delivery, preeclampsia, gestation-induced hypertension and newborn's body weight, as well as the characteristics of the delivery method employed.

Blood glucose and triglyceride assays were done following instructions of commercial kits. The total data recorded were loaded into a single database for further statistical analyses.

2.1 | Statistical analyses

Statistical analyses were done using the Statistical Package for Social Sciences version 15 (SPSS Inc, Chicago, IL, USA). Descriptive statistics are presented as percentages and mean ± standard deviation (SD). Group comparisons for continuous variables were determined by Student t-test and Mann-Whitney U test according to the data distribution profile. We used two-way ANOVA to assess differences between groups in increments in weight, BMI and serum triglyceride of the pregnant women (CG vs IG) and differences between moments of measurement (baseline data vs the one collected at the end of pregnancy). The Chi-squared statistic was used to evaluate differences between proportions. Significance was established at $P \leq 0.05$.

2.2 | Ethical considerations

All study procedures were complied with the ethical standards of the institutional research committee, the Helsinki Declaration of 1964 and its subsequent modifications, or comparable ethical standards. The study protocol was analyzed and approved by the Ethics Committee of the Universidad Nacional del Nordeste (UNNE) (IRB Number: 27/16-10819). All participants included in the study signed their corresponding informed consent.

3 | RESULTS

At the time of the first clinical appointment, clinical and obstetric pregestational background information from the recruited women was recorded as shown in Table 1. It shows that although women included in the CG have a background of lower percentage of obesity, they had a larger percentage of previous macrosomic newborns. No other significant difference was found comparing the other background factors.

When analysing clinical and metabolic variables recorded at the first pregnancy consultation (Table 2), we saw that although we recruited them only by a sequential chronological order, the only significant difference between CG and IG was gestational age (30.2 vs 28.9 weeks; $P \leq 0.002$) and FBG levels (100.6 ± 31.6 vs 92.2 ± 28.9 mg/dL; $P \leq 0.000$), respectively. These two values, however, indicate a GDM diagnosis according to ADA criteria.[27] In both groups, the diagnosis of GDM was confirmed by Oral Glucose Tolerance Test (OGTT).

As an important detail, the QualiGest form records only the woman's body weight and height from these two measurements and the software automatically calculated the BMI. Therefore, due to the availability of these two basic measurements required by the system to determine that parameter, we had BMI data only for 76% and 98% of women from the CG and IG, respectively. These results might suggest that even when data registry was not ideal, it improved in the IG.

At the end of the gestational/delivery period, women in the IG had significantly lower BMI (33.5 ± 5.7 vs 35.8 ± 6.2 Kg/m^2; $P \leq 0.003$) and significantly less weight gain compared to the weight recorded at the first clinical appointment (Table 3 and Figure 1). Concurrently, the newborns in the IG showed significantly lower body weight (3.377.9 ± 591.8 vs 3.484.1 ± 538.3 g; $P \leq 0.0021$), a trend to a lower percentage of macrosomia (12.0% vs 14.8%), a non-significant but lower number of caesarean sections (56.0% vs 60.1%) and a trend to lower serum triglyceride levels (250.1 ± 92.6 vs 285.3 ± 98.2 mg/dL). Also, newborn weight was significantly associated with the mother's weight gain in both the CG and the IG ($r = 0.12$, $P < 0.025$) (Figure 1).

The BMI calculated was 29% (CG) and 69% (IG), whereas triglyceride levels were 3% (CG) and 41% (IG). These differences were considered at the time of statistical evaluation, thereby suggesting a registry improvement associated with the education process.

The number of women who attended reclassification 6 months after delivery was significantly greater in the IG (38% vs 2.7%; $P \leq 0.000$) (Table 3). In the former group, 76.8% had a normal OGTT, 19.5% had prediabetes and 3.7% had already developed T2D. Due to the low percentage of cases in the CG (only seven women attended), no consistent statistical analysis could be done, but the values suggest that the group had a poorer profile (57.1% normal OGTT and 42.9% T2D).

4 | DISCUSSION

Our current IG results show the combination of several favourable outcomes for both mothers and their offspring: a significantly lower BMI and weight gain during the gestational period, a trend towards a lower percentage of serum triglyceride and caesarean sections as well as a significant increase in postnatal attendance to the medical appointment for metabolic assessment/reclassification.

The newborns had a significantly lower body weight associated with a trend to a lower percentage of macrosomia. All together, these

TABLE 1 Pregestational, clinical and obstetric background of the recruited pregnant women

	Control group		Intervention group		
Data recorded	Value	N	Value	N	*P*-value (between groups)
CVRF					
Hypertension (%)	4.9	263	3.0	432	0.193
Obesity (%)	15.6	263	25.0	432	0.003
Smoking (%)	2.7	263	3.0	432	0.790
Dyslipidaemia (%)	0.4	263	0.0	432	0.199
Obstetric history					
Number of previous pregnancies (mean ± SD)	2.3 ± 2.0	258	2.0 ± 1.8	420	0.081
GDM in previous gestations (%)	10.5	209	13.5	347	0.296
Premature newborns (%)	8.5	235	6.8	426	0.424
Preeclampsia (%)	3.0	231	4.5	425	0.366
Family DM background (%)	46.6	251	52.9	423	0.176
Newborn with >4 kg (%)	19.6	240	13.4	426	0.034
HIG in previous gestations (%)	7.2	236	5.2	425	0.289
Eclampsia (%)	0.4	231	0.7	426	0.669

Abbreviations: CVRF, cardiovascular risk factors; GDM, gestational diabetes; HIG, hypertension induced by gestation; DM, diabetes mellitus.

TABLE 2 Characteristics of pregnant women at the time of the first clinical appointment

	Control group		Intervention group		
Parameter	Mean ± SD	N	Mean ± SD	N	*P*-value (between groups)
Mother's age at pregnancy outset (years)	30.8 ± 6.3	259	30.7 ± 6.5	427	0.819
Gestational age at the first consultation (weeks)	30.2 ± 5.1	237	28.9 ± 4.8	396	0.002
Height (cm)	158.9 ± 6.5	221	158.0 ± 6.0	426	0.055
Weight (kg)	75.7 ± 17.4	229	74.6 ± 16.9	424	0.445
BMI (kg/m^2)	29.9 ± 6.1	201	29.8 ± 6.2	423	0.908
SBP (mmHg)	107.5 ± 13.8	240	109.0 ± 13.2	419	0.184
DBP (mmHg)	67.5 ± 9.3	240	68.5 ± 9.6	419	0.160
FBG (mg/dL)	100.6 ± 31.6	220	92.2 ± 16.5	419	0.000
Triglyceride (mg/dL)	225.1 ± 91.8	46	236.2 ± 81.4	296	0.399
Total cholesterol (mg/dL)	229.2 ± 61.6	71	233.8 ± 48.0	368	0.481

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose.

results suggest that our educational intervention combined with management changes (active interaction between primary care and special maternity care) induced a favourable impact on several risk factors and consequently on GDM outcomes related to both the mothers and their offspring.

The lower BMI and weight gain during the gestational period recorded for IG women have been associated with different decreased risk ranges of adverse outcomes depending on pregestational weight.[29] This range went from 14.0 kg (underweight women) to less than 6.0 kg for obesity grade 3 (BMI ≥ 40 kg/m^2).[29] Gestational weight gained outside this range was associated with low and moderate adverse outcomes.[30] A population-based study in the United States of pregnant women with singleton hospital births between 2004 and 2013 found that both low and excess weight gain were associated with severe adverse birth outcomes.[31] In our case, newborn weight was significantly associated with the mother's weight gain ($r = 0.12$, $P < 0.025$).

The combination of maternal BMI, excess gestational weight gain and hyperglycaemia operates as a set of independent factors promoting neonatal adiposity.[32] This evidence supports the favourable

TABLE 3 Outcomes at the end of the gestational/delivery period

	Control group		Intervention group		
Data recorded	Value	N	Value	N	*P*-value (between groups)
Delivery by caesarean (%)	60.1	238	56.0	423	0.311
Newborn (number)	1.2 ± 0.7	219	1.0 ± 0.1	421	0.001
Newborn					
Capurro index (weeks)	38.6 ± 1.4	192	38.4 ± 1.9	422	0.214
Weight (g)	3.484.1 ± 538.3	243	3.377.9 ± 591.8	432	0.021
Macrosomia (%)	14.8	243	12.0	432	0.304
Other complications (%)	7.2	263	8.8	432	0.464
Maternal					
Weight (kg)	88.7 ± 18.4	95	83.8 ± 15.4	304	0.011
BMI (kg/m^2)	35.8 ± 6.2	77	33.5 ± 5.7	300	0.003
Triglyceride (mg/dL)	285.3 ± 98.2	7	250.1 ± 92.6	175	0.361
Complications (%)	8.7	263	7.9	432	0.684
Postpartum reclassification (%)	2.7	263	38.0	432	0.000

Abbreviation: BMI, body mass index.

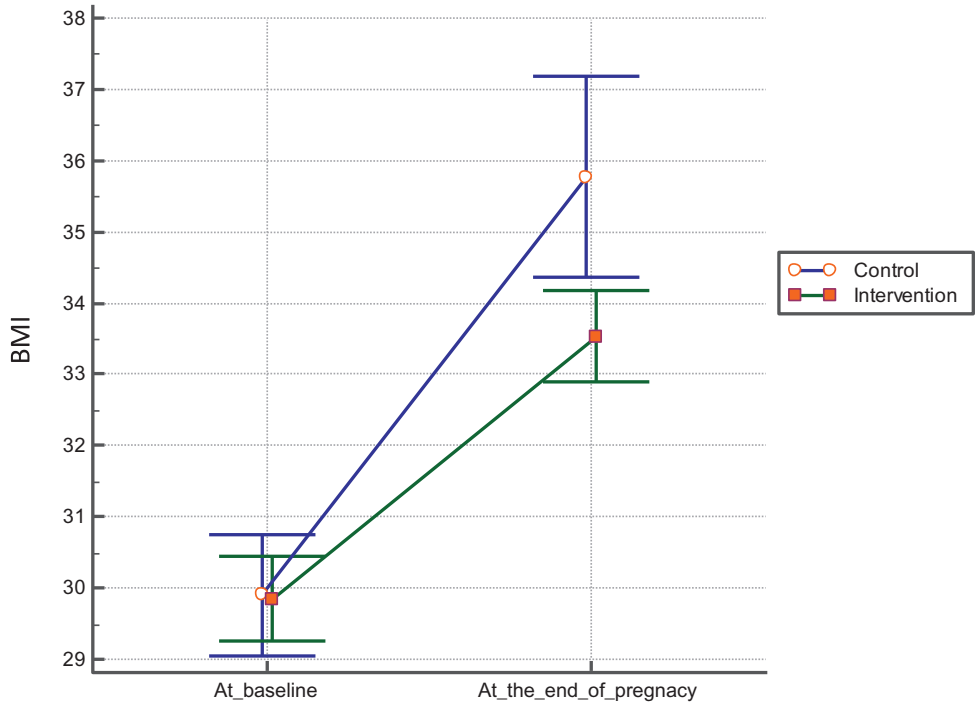

Figure 1 Increase in BMI (baseline vs at the end of pregnancy)

pathogenic role of lower weight gain observed in our IG women. With the same reasoning, a recent report strongly suggests that early GDM screening and diagnosis may be beneficial for tempering gestational weight gain by prescribing and monitoring treatment early in the pregnancy: this program includes the adoption of a healthy lifestyle (meal planning and weight management), as first-line treatment for GDM together with initiating SMBG.[33,34]

A trend of decreased triglyceride was another risk factor ascribed to our educational intervention: though during pregnancy an increase of serum triglyceride occurs normally as a compensatory mechanism to cope with increased demand for metabolic substrates,[35] it has been proposed that impairment of lipid metabolism rather than solely hyperglycaemia is the factor that increases the risk for macrosomia in GDM.[36] Our recent publication which studied the frequency

and pathogenesis of macrosomia in mothers with GDM supports this hypothesis.[37] Although no clear normal cut-off values for serum triglyceride are available for our local population, the lower values recorded in our IG women suggest that they may favour the significantly lower body weight and the lower trend to macrosomia of the offspring currently reported. We are at the moment trying to settle the triglyceride cut-off value for each gestation trimester to overcome such lack of information.

Despite the large pathogenic role of triglyceride in undesirable GDM outcomes, our data show that their measurement is neither systematically prescribed nor fully and systematically recorded. How to change this behaviour may be an excellent area for further research.

Outcomes improvement in our IG could be partly ascribed to the women's adherence to the prescription of a healthy life style; its efficacy concords with previous reports establishing that prevention/treatment of GDM must start with dietary and lifestyle advice, associated with metformin or insulin when the former strategy fails to reach glucose target values. Diabetes education provided to IG might be a prime factor in the induction of this healthy behaviour and the consequent reduction of the risk of having big babies.[38]

The efficiency of the education strategy currently implemented is further supported by the conclusions of the Cochrane meta-analysis, which assures that lifestyle interventions are the primary therapeutic strategy as well as self-monitoring of blood glucose levels.[39] Its success, however, requires trained personnel to provide optimal education and management support such as we implemented in our EduGest study.

Low-quality evidence suggests that women receiving these educational interventions may have more probability of achieving weight goals than those receiving the customary care or only dietary advice. For the infant, moderate-quality evidence shows that lifestyle interventions yield a reduced risk of births with large-for-gestational-age babies and reduced adiposity compared to usual-care or dietary-advice-only babies. On another front, little is known about the cost-effectiveness of these interventions on GDM outcomes for mothers and/or their offspring.[40] This point merits further studies for its assessment and to get stronger evidence of its efficacy.

Postpartum attendance for metabolic reclassification was another successful goal of our intervention: 164 versus seven cases in the IG and CG, respectively. The low attendance observed in the CG was not completely unexpected, because it has been reported that after delivery, women who have had a GDM face difficulties for attending glucose testing postpartum and long-term control visits. These difficulties include fears concerning the risk of developing diabetes and other factors as well. Previous reports have shown that education regarding the risk of developing T2D after having GDM, provided during and after pregnancy, would lower the barriers against testing, thereby enabling earlier diagnosis/treatment management of diabetes and improving long-term outcomes.[40,41] These findings consequently lend further support to our current improvement of postpartum consultations in the IG.

Although we have too few cases to reach a sustainable conclusion, the large difference in percentage of Normal Glucose Tolerance (NGT) (78.6% vs 57.1%) and of T2D (3.7% vs 42.6%) in the IG and CG, respectively, would suggest a favourable impact of our intervention on these results. This suggestion merits further studies to prove the real value of this assumption.

All our results could be ascribed to the educative strategy employed, thereby confirming its effectiveness. In this regard, we initially assume that GDM results from β-cell failure to cope with gestational insulin resistance and that its treatment attempts to prevent/decrease adverse pregnancy outcomes. Consequently, we share and support other authors' conclusion that education is the cornerstone of GDM management, and that well-trained members of the HCTM are the most effective personnel for its implementation.[42]

They also support the hypothesis that this type of intervention implemented at the primary care level closely associated with HCM facilities at an early stage, that is before the pregnancy develops GDM, would enhance the chances for both effective gestation control and post-delivery surveillance to implement preventive care, thereby reducing the risk of undetected early-onset T2D.[43] Furthermore, education given and supported by diabetes peers is associated with many benefits in relation to clinical, behavioural, and psychosocial outcomes. Consequently, when feasible, peer support could be included in order to reap its many potential benefits and cost-effectiveness.[44]

Regarding the future, we might consider that all the above education-induced beneficial effects were obtained by initiating its implementation around the 29-30 gestational weeks; therefore, the results could presumably be significantly improved when education is applied at an earlier stage: ideally, in the first trimester of gestation.

Although our results provide evidence of the improvement of GDM outcomes ascribed to educational intervention, they should be considered with caution due to several weaknesses, namely (a) BMI differences at the end of the gestational period were not obtained/recorded for all the participants, (b) serum triglyceride levels were measured/recorded at that period only for less than 50% of the participants, (c) many of our improvements showed a trend to rather than a significant difference in favour of the IG and (d) our physicians do not spend much time or dedicate careful attention to completely fill out the patient's records; we might reinforce recommendations in our educational program to cope with this problem as suggested by other authors.[45] Implementation of electronic clinical records might also help to overcome this deficiency.[46]

As an aditional limitation, although we have explored food intake (NutriGest) and psychological impact (WHO-5) of GDM, we have presently not described/analysed these results. They merit, however, a deep analysis to their respective role within the education process for a further proximal publication.

Notwithstanding, the consistency of the current data suggests the favourable impact of the integral educational process implemented for the HCTM members and the women with GDM diabetes.

In conclusion, our results suggest that education provided to all the actors involved in the gestation process (women with GDM, members of the HCTM and a well-trained education team), in an integrated combination of primary care level and HCM facilities, is an effective

approach to cope with the socioeconomic burden of the disease both at present and in the long term.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Living Well with Lifestyle Medicine: A group consultation approach to delivering Lifestyle Medicine Intervention in Primary Care

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Abstract

Introduction: Increasing prevalence of chronic disease is raising demands on the healthcare system, and evidence-based cost-effective ways to address these are needed. This project piloted a novel approach of delivering lifestyle medicine in general practice by providing a holistic lifestyle medicine programme to patients at high risk of chronic diseases.

Methods: Eleven patients at high risk of chronic disease participated in a 6-week programme of General Practitioner (GP)-led group consultations, which delivered evidence-based lifestyle education and interventions across all the pillars of lifestyle medicine. Anthropometric data (including weight and body mass index (BMI)) and quality-of-life data (using the EuroQol-5D (EQ-5D-5L) tool) and patient's confidence and motivation were assessed at the beginning and end of the programme to assess impact. Cost-effectiveness was estimated by calculating the cost-per-quality-adjusted-life-year (QALY) for the EQ-5D-5L data.

Results: Seventy-three per cent of participants lost weight, with an average weight loss of 1.7 kg confidence interval (CI), −3.46 to −0.02 kg; $P = 0.048$), which resulted in an average BMI reduction of 0.56 (CI, −1.11 to −0.02; $P = 0.043$) over 6 weeks. Quality of Life scores show improvement, with EuroQol-visual analogue scale (EQ-VAS) score increase of 23 points (CI, +11.82 to +34.18; $P = 0.002$) and EQ-5D-5L scores show reduction in mobility problems, anxiety and depression and pain. Patient's self-rated confidence and motivation to make healthy lifestyle changes improved significantly over the programme.

Conclusions: Delivery of lifestyle medicine intervention via a GP-led group consultation model results in improvement in patients' perceived health and well-being, along with reductions in weight, and reduced problems with mood and pain. Delivery of care in this way is cost-effective. The positive findings from this pilot-scale study support investment in a larger study to further develop and explore delivery of lifestyle medicine intervention in this way.

KEYWORDS
general practice, life style, shared medical appointments

1 | INTRODUCTION

Chronic diseases are increasing; the WHO described non-communicable diseases as the biggest preventable cause of morbidity and mortality.[1] Multiple unhealthy behaviours have a cumulative effect on ill-health; someone in mid-life who smokes, drinks alcohol above the recommended levels, is physically inactive and has a poor diet is four times as likely to die over the next 10 years than someone who has a healthier lifestyle.[2]

Lifestyle medicine uses evidence-based lifestyle therapeutic approaches to prevent, treat and reverse disease. The lifestyle medicine approach includes a whole-food, plant-based diet; regular physical activity; adequate sleep; stress management; avoidance of risky substances and use of non-drug modalities to promote health.[3]

Most lifestyle interventions studied look at the effects of a single variable on the desired outcome. It has been shown that improvement in just one aspect of lifestyle has a significant improvement on morbidity and mortality, regardless of which aspect of health behaviour is improved. The same study showed that improving just one aspect of health behaviour had significant cost benefit and was cost-effective for the health economy.[4]

However, the reality is much more complex; in any one individual, multiple lifestyle factors interact interdependently to influence the overall health outcome. Thus, trying to correct any one particular factor may be confounded by the effects of others. For instance, patients will often complain that they cannot lose weight despite regular exercise, even above and beyond the recommended levels; in this scenario, it is often the case that other compounding factors are at play such as stress, poor diet, lack of sleep or psychological factors.

Moreover, for many, there are quite significant changes that need to be made to multiple areas of lifestyle. By trying to get any one aspect of lifestyle 'right' before addressing others, it is setting a high, possibly unmanageable, target. It is more realistic to set 'smart' goals in multiple areas making several small, manageable, realistic targets across a broad base, rather than one single big goal. Instead of prescriptive or didactic advice, patients can be presented with a range of multiple evidence-based lifestyle changes to choose from to suit their needs. This empowers patients to make an individualized 'lifestyle action plan' as increased patient autonomy has been shown to lead to improved health.[5] Initial changes will lead to some measurable improvements, which may then inspire onwards continuation of positive change to build on their initial successes.

A great deal of time would be required to discuss the wide number of topics encompassed by all the pillars of a Lifestyle medicine, especially when we also need to develop practical ways of implementing positive changes. Currently, time constraints within primary care make this very difficult in individual consultations. Group consultation or shared medical appointment (SMA) approaches have been shown to be an efficient way of delivering care, increasing individuals' face-time with the clinician, with the added benefit of peer support from other group members. In the United Kingdom so far, SMAs have mainly been used to target a single condition (eg, asthma or diabetes), but they may also be an effective way to deliver lifestyle interventions.[6–10]

The design of this series of group consultations is purposely to be led by a GP with specialist expertise in lifestyle medicine. There are several benefits to this approach. Firstly, the content is expertly curated, and robustly evidence based. Secondly, it is well recognised that the interaction between doctor and patient in itself has a therapeutic effect, and studies have suggested that this may account for 30-40% of benefits gained.[11] A GP-led service will facilitate patient involvement by emphasizing the importance of lifestyle advice, where previous advice given in routine clinical care settings may have not been heeded. GPs are experienced in dealing with complex multi-morbidity and conditions with complex multifactorial contributing causes, which is frequently the case with lifestyle-related conditions. The GP can draw on their clinical experience to individualise the support given during the sessions as appropriate. This could involve proactively identifying patients who may need either extra support, and facilitate appropriate early interventions. More hopefully, for patients who are progressing well, they can be identified for down titration of current treatment and these changes can be made by the clinician without need for separate contacts with the patient's primary care team.

The purpose of this paper, therefore, is to describe an innovative group consultation programme that was designed to provide holistic lifestyle interventions in a time effective way. This took place in early 2020 in County Durham, England. The paper also sets outs the results of this pilot-scale project in terms of both the physiological outcomes and patient perceptions. The relationships between the variables within and between these two areas are also examined.

There is increasing emphasis on prevention of disease, rather than intervention once disease is established. Early intervention can reduce the progression to long-term chronic conditions for those at high risk, in a cost-effective way.[4,12] Moreover, lifestyle medicine interventions in primary care have been shown to be cost-effective.[13] Our paper also finds that lifestyle medicine intervention in primary care is cost-effective; thus, this pilot study may be used to inform the future development of such programmes, and its findings support investment in a much larger scale study to explore such interventions.

1.1 | Aims

The programme aimed to improve the patients' well-being, their confidence and motivation to make healthier lifestyle choices by attendance at a series of group consultations addressing Lifestyle medicine. Objective physiological measurements were assessed; namely weight,

blood pressure, BMI and waist circumference. Whether attendance at a Lifestyle medicine intervention improved the patient's feeling of well-being was assessed. The acceptability of group consultations for delivering this kind of intervention in terms of patient satisfaction was also examined.

2 | METHODS

2.1 | Patient recruitment

Patients were recruited from the patient population registered with the author's town-centre general practice in County Durham, a large practice (approximately 12,000 patients) serving a population with a high index of deprivation. The patient population targeted were individuals at high risk of chronic disease, that is overweight, obesity, hypertension and pre-diabetes. Patients who already had established type II diabetes were also accepted. The course was advertised within the practice, on the practice website and clinicians were encouraged to promote it to patients who they felt may benefit from this intervention. Patients could also self-refer. All patients were contacted by a healthcare assistant prior to commencing the course to explain the outline of the programme and allow potential participants the opportunity to ask for information. No patients were excluded from taking part in the programme, and places in the group were offered on a first-come basis.

2.2 | Intervention

The programme consisted of six face-to-face sessions, lasting 90 min each, between January 2020 and March 2020. It was intended that the group would consist of approximately 12 participants. Sessions were led by a GP with support from a practice nurse and a healthcare assistant.

Each session consisted of educational material being presented, together with group activities and opportunities for patients to ask questions and interact. The structure of the course was based around the key pillars of lifestyle medicine, namely nutrition, physical activity, sleep and stress management. Each week followed a dedicated theme, designed to focus on one of these pillars. The first week provided an overview and introduction, and the last week incorporating a summation and focusing on planning for continued lifestyle changes in the future by creating individualised action plans. Sessions were designed in a bespoke fashion; the aims and objectives of each session's content were tailored to the needs identified by the patients and clinician at the beginning of the course, and from feedback provided by patients after each session. Each session followed a similar structure, with a welcoming activity, outlining the aims and objectives for the session followed by a short presentation of relevant educational information and discussion of the facts and evidence behind the area of lifestyle medicine being discussed. This was built on with group discussion and interactive activities giving the patients opportunity to consider the material discussed. Provision was made for patients to have advice individualised and tailored to their particular health circumstances.

In each session, we gave participants the opportunity to have their weight and blood pressure checked. Alongside the face-to-face sessions, there was ongoing online support available via a closed private group on social media for patients to interact with each other, to provide peer-to-peer support and also ask questions of the clinicians. Patients were encouraged to contact the clinician in-between sessions via this online group with any questions or needs to be addressed in the next sessions.

The programme was designed to build connections with the wider health and well-being community. Throughout the programme, patients were signposted to local community provision and resources which could support them in their ongoing lifestyle changes. For example in session 3, focusing on physical activity, we liaised with local fitness providers. Several of the coaches attended the session to meet the participants and encourage them join community activity programmes subsequently.

2.3 | Evaluation

Prior to commencing the course, patient consent was sought for use of anonymised data to analyse the course outcomes. Patients were provided with a patient information leaflet regarding the programme and data use, and provided written consent for use of their anonymised data.

Demographic data were recorded. Patient's height, weight, BMI and blood pressure were recorded each week. The values of these physiological measures at the beginning and the end of the programme were compared.

The patient's quality of life and self-perceived wellness was measured using the EQ-5D-5L and EQ-VAS tool. The difference in scores at the beginning and the end of the programme was compared; both the overall health EQ-VAS score and each of the five individual dimensions of the EQ-5D-5L questionnaire were analysed. To give numerical values that could be compared, each dimension of the EQ-5D-5L tool (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) was considered separately. For each dimension, the answers were given a numerical value between one and five, where the best perceived function or health level was given a score of one and the worst level was given a score of five. Thus, an improvement of the patient's perception of their health status in each dimension, with reduced levels of problems, would result in a decrease in their score. The EQ-VAS tool asks patients to rate their own perceived level of health from 0 (worst health imaginable) to 100 (best health imaginable); thus, an improvement in the patient's perceived health results in an increased EQ-VAS score.

Patient's self-rated motivation to make lifestyle changes, confidence to make lifestyle changes and how they perceived the importance of making lifestyle changes were assessed using questionnaires at the beginning and the end of the course. Each aspect was scored on a scale of 0-10 (0 being not at all confident/motivated/important to 10 being

extremely confident/motivated/important). The difference between these values at the beginning and end of the course was assessed and compared.

At the end of the programme, patients were additionally asked how they perceived their change in confidence and motivation, on a scale of 0 (decreased a lot) to 10 (increased a lot).

Participants were also asked how likely they were to make a change to their lifestyle as a result of attending the course, giving a rating of 0 (not at all likely) to 10 (extremely likely).

Pre- and post-programme scores were compared using the paired samples *t*-test.

Qualitative feedback was sought from all the patients both at the end of each session and at the end of the course overall. The family and friends test was asked of all participants at the end of the course.

In the initial design of the research aspect of the programme, it was intended that all participants would be followed up at 6 months and 12 months to see if they have sustained any changes seen, and to assess any longer term benefits achieved in terms of outcomes. It was also planned that the pilot course would have been run twice with two cohorts of patients to provide a larger patient group for assessment. Unfortunately, shortly after completion of the first round of the pilot scheme, the impact of the global coronavirus pandemic meant that further face-to-face group consultations could not be undertaken. Further follow-up to assess the long-term benefits of the programme was not carried out, as the effect of the pandemic is such a discontinuity in health terms that it is very unlikely the results from any further follow-up would be meaningful in comparison with those from the initial programme.

3 | RESULTS

3.1 | Demographics and participation

Thirteen patients signed up to participate in the course. Most patients were female (82% F vs 18% M). Average age was 46.5 years, ranging from 27 to 63 years.

Patient engagement and attendance was very good. Of the 13 patients initially registered, 11 patients attended four or more of the six sessions, with most of these (nine patients, 82%) attending all or five out of the six sessions; the remainder (two patients, 18%) attended four out of six sessions. The average number of sessions attended was 5.3. Two patients attended only one session and then withdrew from the programme, therefore their data were not included in the final analysis of results.

The patients who attended the course were primarily female, this is in keeping with the higher rates of engagement with healthcare for women compared to men that are seen in other areas.

Patient attendance and participation in sessions was extremely high and maintained throughout the course. This is reflected in the high motivation scores, which may indicate patients are committed to maintenance of their health behaviour change, which will lead to further improvements in health after the course has completed, leading to long-term health improvement.

Patients who made the commitment to attend a course with multiple sessions are already demonstrating significant motivation and dedication to making health improvement; they are already at the action stage of making change.[14] This high level of motivation will contribute to their positive outcomes.[15] More work will need to be done to look at how to engage patients who are earlier in the stages of change model.

3.2 | Physiological measurements outcomes

Table 1 sets out the differences between the mean values of the physiological measures at the start and the end of the programme. The table shows that weight and BMI are the only measures where the difference between mean values is statistically significant at the 5% level. This is also illustrated in Figure 1 where the 95% confidence intervals (CI) are shown as error bars on the mean differences.

Most of the patients lost weight (eight patients, 73%). Average starting weight was 110.0 kg and average finishing weight at week 6 was 108.3 kg, giving a mean weight loss of 1.7 kg (CI, −3.46 to −0.02 kg; $P = 0.048$) over 6 weeks. The mean weight loss for the patients who reduced weight was around 2.5%. Average starting BMI was 38.5 and average BMI at the end of the programme was 37.9. This gives a mean reduction in BMI of 0.56 (CI, −1.11 to −0.02; $P = 0.043$). It is to be expected that mean difference for BMI is also significant because weight is the numerator in the calculation of BMI.

The reduction in weight and BMI in the patients over the course was statistically significant. This was achieved over a fairly short time frame and further follow-up would be required to see if this improvement continued and whether it was sustained over the longer term.

Weight loss amounts were small, but this is to be expected for a short programme. Intensive lifestyle medicine programmes elsewhere have seen average weight loss of 8 kg over 6 months.[16] Therefore, the weight reductions seen in the cohort of patients in this programme are consistent with results seen in other interventions.

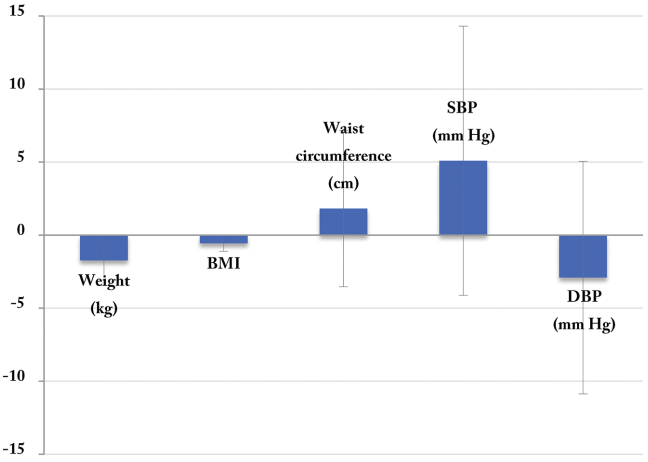

FIGURE 1 Differences between mean values of physiological measurements at baseline and follow-up

TABLE 1 Significance test of differences between mean values of physiological measurements at baseline and follow-up

Measure	Mean		Difference	SD	SE	95% Confidence interval		Significance test[a,b]	
	Baseline	Follow-up				Lower	Upper	t-statistic	P-value
Weight (kg)	110.045	108.309	−1.736	2.563	0.773	−3.458	−0.015	−2.247	0.0484
Body Mass Index	38.482	37.918	−0.564	0.805	0.243	−1.105	−0.023	−2.321	0.0427
Waist circumference (cm)	111.000	112.818	1.818	7.973	2.404	−3.538	7.174	0.756	0.4669 (NS)
Systolic BP (mm Hg)	121.818	126.909	5.091	13.722	4.137	−4.128	14.309	1.230	0.2467 (NS)
Diastolic BP (mm Hg)	75.455	72.545	−2.909	11.844	3.571	−10.866	5.048	−0.815	0.4343 (NS)

[a]Significance test is for a two-tailed test of the difference at the 5% significance level with 10 degrees of freedom.
[b]NS = not significant at the 5% level ($|t| < 2.228$, ie P-value > 0.05).
SD = standard deviation, SE = standard error.

TABLE 2 Distribution of EQ-5D-5L dimension responses at baseline and follow-up

Dimension	Baseline		Follow-up	
	n	(%)	n	(%)
Mobility				
No problems	4	(36.4)	6	(54.5)
Slight problems	5	(45.5)	5	(45.5)
Moderate problems	2	(18.2)	0	(0.0)
Severe problems	0	(0.0)	0	(0.0)
Unable to walk about	0	(0.0)	0	(0.0)
Self-care				
No problems	10	(90.9)	10	(90.9)
Slight problems	0	(0.0)	1	(9.1)
Moderate problems	1	(9.1)	0	(0.0)
Severe problems	0	(0.0)	0	(0.0)
Unable to wash or dress	0	(0.0)	0	(0.0)
Usual activities				
No problems	3	(27.3)	4	(36.4)
Slight problems	7	(63.6)	5	(45.5)
Moderate problems	1	(9.1)	2	(18.2)
Severe problems	0	(0.0)	0	(0.0)
Unable to do usual activities	0	(0.0)	0	(0.0)
Pain/discomfort				
No pain/discomfort	2	(18.2)	3	(27.3)
Slight pain/discomfort	2	(18.2)	6	(54.5)
Moderate pain/discomfort	4	(36.4)	2	(18.2)
Severe pain/discomfort	3	(27.3)	0	(0.0)
Extreme pain/discomfort	0	(0.0)	0	(0.0)
Anxiety/depression				
Not anxious/depressed	0	(0.0)	3	(27.3)
Slightly anxious/depressed	1	(9.1)	5	(45.5)
Moderately anxious/depressed	6	(54.5)	2	(18.2)
Severely anxious/depressed	2	(18.2)	0	(0.0)
Extremely anxious/depressed	2	(18.2)	1	(9.1)

Even small changes in weight may still have a significant health benefit. A weight loss of only 3–5% of initial body weight can lead to improvements in triglycerides, glucose, Hba1c and reduce risk of developing T2DM.[17]

Measurement of waist circumference is recognised as being less reliable at BMI > 35, which was the case for the majority of these patients; this may contribute to the lack of change seen in the patients' waist circumference results.

3.3 | Quality of life

The data from the EQ-5D-5L questionnaire are shown in Table 2 where the number of actual responses given for each dimension of the

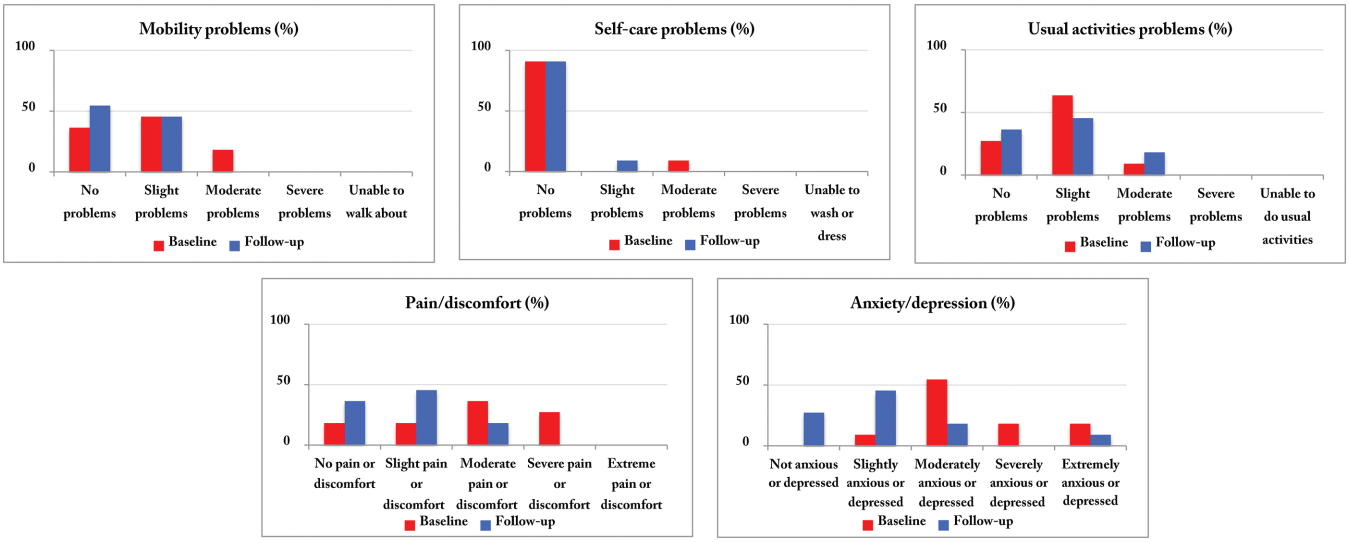

FIGURE 2 Proportion of responses by level of severity for EQ-5D-5L dimensions at baseline and follow-up

questionnaire are given, and the proportion of responses in each dimension and the change between the beginning and the end of the programme are illustrated in Figure 2.

Table 3 sets out the differences between the mean values of the EQ-VAS and EQ-5D-5L measures at the start and the end of the programme.

The average pre-course EQ-VAS score is 46.4, and the average post-course EQ-VAS score is 69.4. This represents an improvement of 23 points on the self-rating overall health scale (CI, +11.82 to +34.18; $P = 0.002$). This is a significant difference.

The components of the EQ-5D-5L questionnaire were also considered individually. For mobility, the mean pre-course score is 1.82 and the mean mobility score post-course is 1.46, showing mean reduction in mobility problems with an improvement of −0.36 (CI, −0.71 to −0.03; $P = 0.038$). Regarding pain, the mean pre-course score is 2.73 and the mean pain score post-course is 1.91, showing a mean improvement of −0.82 (CI, −1.32 to −0.31; $P = 0.005$). For anxiety/depression scores, the mean pre-course score is 3.46 and the mean anxiety/depression post-course score is 2.18, showing a mean improvement of −1.27 (CI, −1.71 to −0.84; $P = 0.0001$). The differences for the dimensions of self-care and usual activity are not significant.

Figure 3 illustrates the differences in the mean values of EQ-VAS and EQ-5D-5L dimensions scores between the beginning and the end of the programme. Figure 4 demonstrates the change in mean values of the scores and their significance can be seen from the error bars.

Patients had a greatly improved perception of their own health following participation in the course sessions. The improvement in the EQ-VAS score is supported by statistically significant improvements in three out of the five components of the EQ-5D-5L score, for anxiety/depression, pain and mobility. Improvements in these scores correlate with better quality of life for the patient. This is important as it may correlate with reduction of morbidity, and thus also result in reduced healthcare burden for the individual, which then leads to reduced healthcare costs overall.

TABLE 3 Significance test of differences between mean values of EQ VAS and EQ-5D-5L dimensions scores at baseline and follow-up

	Mean					95% Confidence interval		Significance test[a,b]		
	Baseline	Follow-up	Difference	SD	SE	Lower	Upper	*t*-statistic	*P*-value	
EQ VAS (Min = 0; Max = 100)										
Overall health	46.364	69.364	23.000	16.643	5.018	11.819	34.181	4.583	0.0016	
EQ-5D-5L (Min = 1; Max = 5)										
Mobility	1.818	1.455	−0.364	0.505	0.152	−0.703	−0.025	−2.390	0.0379	
Self-care problems	1.182	1.091	−0.091	0.302	0.091	−0.293	0.112	−1.000	0.3409	(NS)
Usual activities problems	1.818	1.818	0.000	0.775	0.234	−0.520	0.520	0.000	1.0000	(NS)
Pain/discomfort	2.727	1.909	−0.818	0.751	0.226	−1.323	−0.314	−3.614	0.0047	
Anxiety/depression	3.455	2.182	−1.273	0.647	0.195	−1.707	−0.838	−6.528	0.0001	

[a]Significance test is for a two-tailed test of the difference at the 5% significance level with 10 degrees of freedom.
[b]NS = not significant at the 5% level ($|t| < 2.228$, ie P-value > 0.05).
SD = standard deviation, SE = standard error.

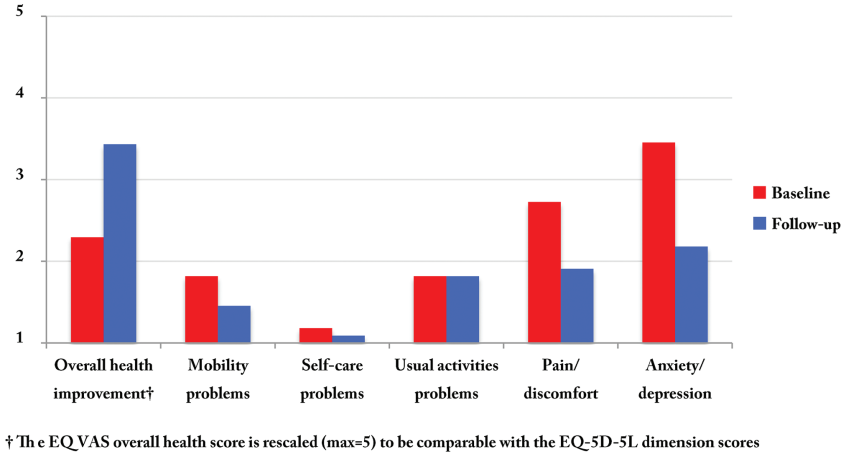

FIGURE 3 Mean values of EQ-VAS and EQ-5D-5L dimensions scores

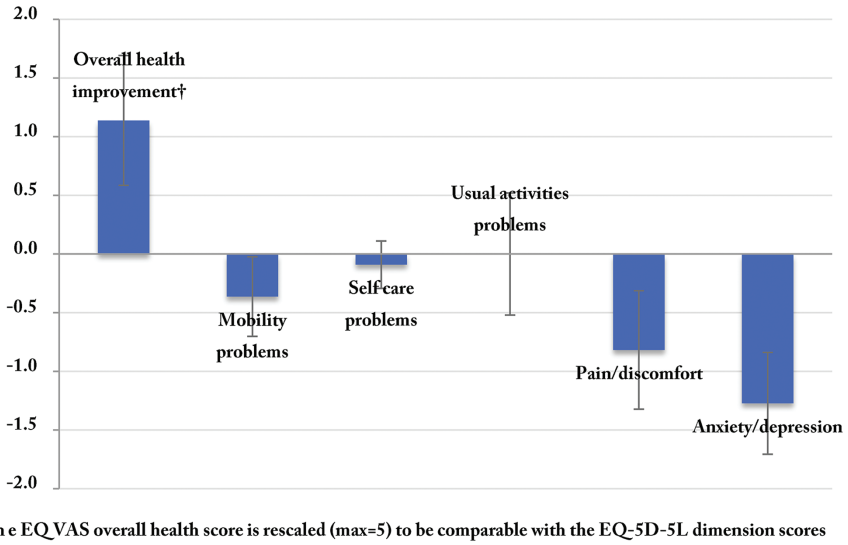

FIGURE 4 Differences between mean values of EQ-VAS and EQ-5D-5L dimensions scores at baseline and follow-up

3.4 | Patient confidence and motivation to make lifestyle changes

Figure 5 shows the mean values of the patient's self-reported scores for confidence and motivation to make lifestyle changes, and for the importance of making such changes, at the beginning and end of the programme. Table 4 and Figure 6 set out the significance test of differences between mean values of patient perceptions scores at baseline and follow-up.

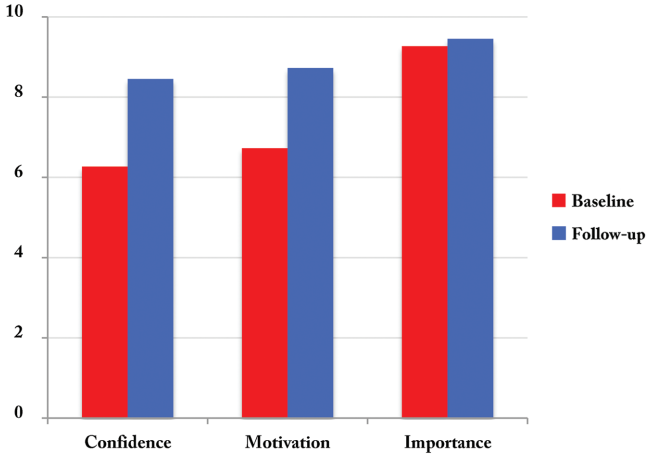

FIGURE 5 Mean values of patient perceptions scores

For patient's confidence to make lifestyle changes, the mean score at the beginning of the course was 6.27 and the mean score at the end of the course was 8.46. The difference between starting and finishing scores is an increase in confidence score of +2.18 (CI, +0.72 to +3.65; $P = 0.008$). For patient motivation to make lifestyle changes, the mean score at the beginning of the programme was 6.73 and the main score at the end of the programme was 8.73. The difference between starting and finishing scores is an increase in motivation score of +2.0 (CI, +0.30 to +3.70; $P = .026$). The increases in the patients' scores for confidence and motivation to make lifestyle changes are both significant.

The increase in the patients' perceived importance in making lifestyle changes is not significant. However, this is not really surprising as at the beginning of the programme the mean scores showed that patients already rated the importance of making lifestyle changes very highly, and this did not change over the duration of the programme.

TABLE 4 Significance test of differences between mean values of patient perceptions scores at baseline and follow-up

	Mean[a]					95% Confidence interval		Significance test[b,c]		
	Baseline	Follow-up	Difference	SD	SE	Lower	Upper	*t*-statistic	*P*-value	
Confidence	6.273	8.455	2.182	2.183	0.658	0.716	3.648	3.315	0.008	
Motivation	6.727	8.727	2.000	2.530	0.763	0.300	3.700	2.622	0.026	
Importance	9.273	9.455	0.182	0.982	0.296	−0.478	0.841	0.614	0.553	(NS)

[a]Patient perceptions scores: Min = 0; Max = 10.
[b]Significance test is for a two-tailed test of the difference at the 5% significance level with 10 degrees of freedom.
[c]NS = not significant at the 5% level ($|t| < 2.228$, ie P-value > 0.05).
SD = standard deviation, SE = standard error.

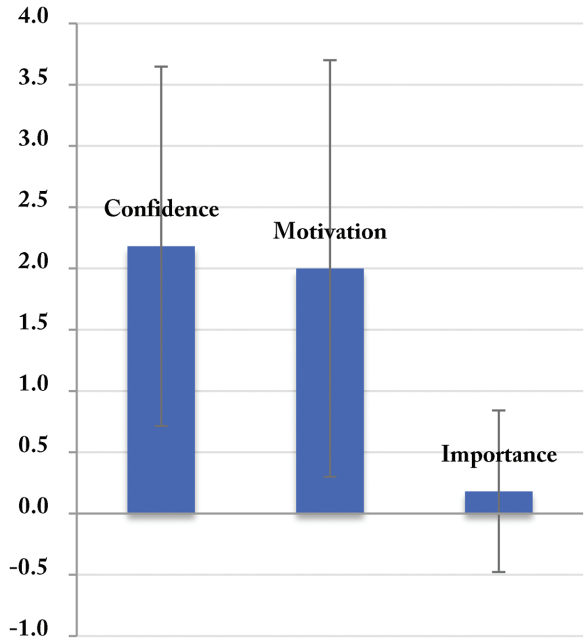

FIGURE 6 Differences between mean values of patient perceptions scores at baseline and follow-up

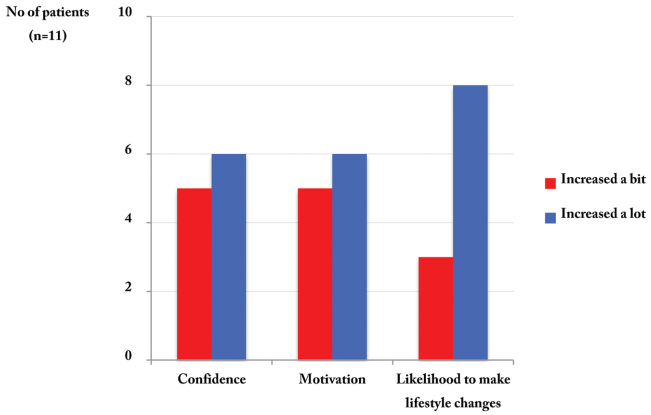

FIGURE 7 Self-rated changes in patient perceptions

3.5 | Patient self-rated perception of confidence, motivation and likelihood to change

At the end of the programme, patients were also asked to self-rate the change in their confidence and motivation as a result of their attendance, and the likelihood that they would make changes as a result. Figure 7 shows that all patients reported that their confidence increased as a result of attendance: five out of 11 patients reported that their confidence 'increased a bit', and six out of 11 patients reported that their confidence 'increased a lot'. Similarly, all of the patients reported an increase in their motivation: five patients reported that their motivation 'increased a bit' and six patients reported that their motivation 'increased a lot' as a result of attending the programme. All patients reported that they were either 'likely' or 'very likely' to make changes to their lifestyle to improve their health after attending the programme.

3.6 | Patient satisfaction

Patients were asked to rate how useful they found the course; in response, all rated the course as 'very useful' (4/11, 36%) or 'extremely useful' (7/11, 64%). Patients were also asked to state how likely they were to recommend this programme to friends and family. Patient satisfaction was very high; all patients reported finding the course either 'very useful' or 'extremely useful', and all reported themselves as 'extremely likely' to recommend it to family and friends. This indicates a high level of acceptability for delivering health-related lifestyle advice in this format.

3.7 | Relationship between patient health perceptions and weight

The above results raise the possibility that patients' perceptions of their overall health respond directly to changes in their weight or BMI, especially as these measures are readily understood and open to self-monitoring by patients. Regression analysis was used to investigate whether such a relationship could be discerned, even in this small sample of 11 patients. Details of the analysis are set out in the Appendix A.

The regression analysis shows that there is a statistically significant relationship between the change in patients' perceptions of their

overall health, as given by their EQ VAS scores, and the percentage change in their weight over the 6-week period. The estimated relationship implies that a 1% reduction in weight is associated with an increase in the perceived overall health score of around five points. The analysis was repeated using the percentage change in the patients' BMI instead and similar results were obtained, as would be expected because weight is also the numerator in the calculation of BMI. Here, a 1% reduction in BMI results in about a six-point increase in the overall health score.

However, in statistical terms, each of the estimated relationships only explains about a third of the variation in the overall health score, suggesting that other factors are likely to be involved. The relationships were, therefore, re-estimated to examine the potential effects of demographic factors. Gender, age and marital status were tested, but none of these factors were found to be significant.

3.8 | Relationships among confidence, motivation and health perceptions

The previous results also suggest that the increase in both the confidence and motivation of patients to make lifestyle changes by the end of the programme might have resulted directly from their perceptions of the increase in their overall health. Regression analysis was again used to test whether such relationships could be detected, even in this small sample. Details of the analysis are set out in the Appendix A.

The analysis shows that there are statistically significant relationships between the changes in the patients' scores for both confidence and motivation, and the changes in their EQ VAS scores over the 6-week period.

As the maximum EQ VAS score is 100 and that of the scores for both confidence and motivation is 10, the results imply that an estimated increase of 10 points in the EQ VAS score is associated with an increase of similar proportions for the motivation score, whereas for the confidence score it is around 30% lower. The variation in the EQ VAS score accounts for around 43% of the variation in the confidence score and two thirds of the variation in the motivation scores. The potential effect of demographic factors was analysed but, as before, none were found to be significant. The effect of the patients' change in weight on their confidence and motivation scores was also examined because it appears to be a significant factor affecting perceptions of overall health, but it was not found to be significant in these relationships. Presumably, this is because it is unlikely to be the only factor involved in the formation of health perceptions.

3.9 | Cost-effectiveness

The cost-effectiveness of the programme is analysed by calculating its Cost per QALY (Quality-Adjusted Life Year) ratio based on an economic assessment of health service costs and the responses to the EQ-5D-5L questionnaires. The cost calculations represent the incremental cost of the programme beyond the continuation of existing pharmacological treatments and no other interventions.

TABLE 5 Incremental cost of the programme

	Hours	Hourly rate	
		£	£
Staff costs			
General practitioner	24	75	1800
Nurse	12	28	336
Health care assistant	12	20	240
Administration			150
Facilities			
Meeting room	24	25	600
Supplies and materials			74
Total			3200
Cost/Patient			290

3.10 | Resource costs

Although no additional financial costs were incurred, as all staff costs were accommodated within existing workloads and existing rooms and facilities were used, an economic assessment requires the opportunity cost of the health service resources used by the programme to be estimated. The incremental resource costs are summarised in Table 5. The costs were incurred over a 7-week period and so have not been discounted. The initial investment in design and development costs is excluded as it is non-recurring and would not, therefore, be repeated in further programmes. Societal costs were negligible.

3.11 | EQ-5D-5L and QALYs

HRQoL (Health Related Quality of Life) utilities at the beginning and the end of the programme were calculated using the responses to the EQ-5D-5L questionnaires. The calculation method followed the procedure recommended by NICE (National Institute for Health and Care Excellence). Value weights are applied to the patients' scores for each of the five levels in each of the five dimensions in the questionnaire, the total of which is then the patient's HRQoL utility at that time. Unfortunately, at the time of writing a reliable EQ-5D-5L value set is not available, so NICE has recommended that the earlier EQ-5D-3L value set be used and converted to a 5L value set using the mapping function derived by Van Hout et al.[18,19] EQ-5D-5L Index Values based on this mapping function and obtained from the EuroQol crosswalk calculator[20] were, therefore, used as the patients' HRQoL utilities.

The means of the patient HRQoL utilities at the beginning and the end of the programme were 0.518 and 0.709, and the 0.191 improvement between these means was statistically significant (CI, +0.08 to +0.30; $P = 0.004$). Consequently, over the 35 days of the programme, the total QALY's gained (assuming a linear rate of improvement) was

TABLE 6 Illustrative calculations of QALYs gained and cost per QALY

	Actual	Total after decay period	
	After 35 days	18 months	4 years
QALYs gained	0.101	1.674	4.297
Cost per QALY (£)	31813	1911	745

0.101, giving a cost per QALY of nearly £32k, but this figure assumes that the benefit of the programme ceases at the end of the intervention, which is not the case. There will clearly be a continuing health benefit beyond the end of this programme leading to additional QALYs, but it would be unduly optimistic to assume this level of improvement would continue for the remainder of the patients expected lives without any further intervention. Although no follow-up data on the patients are available for the reasons explained above, it is possible to make some illustrative calculations of the future health gains based on research into the rate of decay of benefits obtained from other intensive lifestyle interventions.

A study following 348 participants in a 4-week educational course in Rockford, Illinois found that although the biggest improvements in behaviour occurred at 6 weeks, there were still significant improvements after 18 months.[20] Another study of 248 individuals in a 30-day lifestyle intervention programme in Hawara, New Zealand found statistically significant improvements in biometrics at the end of the programme, and that after 3-5 years the weight reduction, although smaller, was still significant, amounting to about 35% of the mean weight reduction achieved at the end of the programme.[21]

Illustrative calculations of the potential QALYs that might be gained from this programme with decay periods of 18 months and 4 years have been made using the 'area under the curve' method and were based on the relatively conservative assumptions that the benefit wholly disappears at the end of the relevant period and that the rate of decay is constant.[22] The results are set out in Table 6.

3.12 | Cost per QALY

If the benefits of the programme are maintained over the long term, then it is possible that existing pharmacological treatments could be reduced, and in some cases eliminated. Even if there are further more limited follow-up programmes to constrain behaviour decay, the (undiscounted) cost per QALY estimates in Table 6 suggest that the Incremental Cost Effectiveness Ratio of this kind of programme could be within the current NICE threshold of £20-30k for new technologies. For the conservative estimate that effect would be disappeared by 18 months, the cost per QALY is £1911, and if effect is maintained up to 4 years, as seen in other studies, cost per QALY reduces to £745, both of which are very much below the NICE threshold. Indeed, it is possible that this intervention could dominate existing treatments by offering greater health benefits at lower cost.

3.13 | Cost benefits

Cost benefits from improved health outcomes include reduced medication costs, reduced need for follow-up appointments and reduced need for hospital specialist care. Cost benefit such as medication savings would be likely seen over longer term, rather than immediately during the programme itself because sustained improvements are needed for down-titration of most medications. It was not possible to carry out this longer term follow-up due to reasons mentioned above, but it is possible that these cost benefits could more than off-set the costs incurred, particularly for diabetic patients if they can achieve remission.

4 | DISCUSSION

This programme was specifically designed to be led by a physician with an interest in the area of Lifestyle Medicine. This is important because having a GP leading the programme means that the complex multi-morbidity of patients with multiple long-term conditions can be taken into account and tailored specific advice can be offered and adjusted according to patient's individual need. Medication adjustment and review relevant to the lifestyle changes made can be done responsively during group consultations, without need for additional appointments, thus reducing the burden on the wider healthcare system. Specialist clinical leadership provides support, education and training and supervision to allied health professionals involved in the delivery of sessions.

This programme helped patients make adjustments to the areas of lifestyle which they identified as their most pressing need. Equal emphasis was given to each pillar of lifestyle medicine, and patients were encouraged to make changes which suited their individual goals. This holistic approach resulted in improvement in overall well-being.

This is important because educating participants on health behaviours could change their locus of control beliefs from external to internal. There is significant improvement in both the patient's confidence in their ability and their motivation to make lifestyle changes to improve their health from the beginning to the end of the programme. This would predict better future outcomes by allowing the participant to feel in control of their health, rather than having the perception that their health problems stem from outside, unchangeable influences. Improving the internal locus of control heightens ability to cope with events such as lifestyle change, empowering and giving confidence.[23,24] In turn this may lead on to sustained longer term health improvement.

There is a complex inter-relationship among the patients' perception of well-being, their confidence and motivation to make lifestyle changes and their objective physiological parameters. This is confirmed by the regression results, which demonstrate a positive relationship between health perception and reductions in weight.

Although simple regression results from a very small-scale pilot programme are not conclusive, they suggest that weight plays a significant role in the formation of patients' perceptions about their

Case study – Patient journey

Mr N is a 59-year-old man who joined the programme as part of a new year resolution to get in control of his health. Prior to starting the programme, he had uncontrolled diabetes, fatty liver, hyperlipidaemia, hypertension (controlled with medication), CKD, obesity class 1, OSA and joint pains which limited his activity to walking less than half a miles at a time.

At the time of commencing the programme, his vital signs were as follows: weight = 105.1 kg, BMI = 34.2, BP = 118/70 (on medication) and Hba1c = 116. His medication included long-acting insulin (tuojeo) 80 units OD, plus short-acting insulin (novorapid) with meals, atorvastatin and candesartan.

Mr N attended five out of six sessions of the course, and actively engaged with the online group. He had also joined weight watchers for ongoing peer support and access to regular weigh-ins, although he did report that he did not like the weight-watcher's 'diet' and preferred to follow a low-carbohydrate approach and advice given during the programme.

Throughout the programme, his blood sugar levels were monitored by the patient, and his insulin dose was down-titrated by the programme's GP clinical lead (CG) to keep in line with his blood sugar levels, as his requirements changed following conversion to a lower carbohydrate diet.

Halfway through the course his anti-hypertensive medication (candesartan) was stopped by CG, as although his clinic readings were normal, he developed episodes of symptomatic hypotension, with home readings of <100 mmHg systolic at the time.

By the end of the course, weight was down to 99.7 kg (weight loss of 5.4 kg), BMI was 30.7 and BP was 126/68 (off medication).

Mr N had a further routine diabetic follow-up appointment in May 2020: he was able to stop his insulin (tuojeo) at that point. Vital signs in May 2020 were as follows: weight = 90.3 kg, BMI = 27.8 (overweight) and Hba1c = 47. He had moved from being class1 obese to overweight, and from uncontrolled diabetes into the pre-diabetic range. He reported feeling much better, having increased his physical activity and going to the gym regularly (three to four times per week). His joint pains had improved and he was attending the ability to walk briskly for 1.5 miles. He also noted that his sleep was improved. Mr N reported that the programme had helped his understanding of why different aspects of lifestyle were important, which helped his motivation for making changes. At his most recent review, he expressed an intention to maintain these changes, with the hope of continuing to lose some more weight, increase his activity levels further and maintain remission of his diabetes.

overall health. The results also indicate a correlation between the participants' health perceptions and their confidence and motivation. Taken together, these results are promising as they suggest that a programme like this, by improving patients' lifestyle practices and reducing their weight, can have a significant effect on patients' health perceptions. In turn, improved health perceptions could directly increase their confidence and motivation to make more lifestyle changes in the future. The theory of positive psychology suggests that small positive changes are important for patient confidence and motivation, so this initial positive outcome with regard to weight loss may help with continued patient motivation and confidence to continue to maintain positive lifestyle changes.

The results of the statistical analysis reinforce the case for a more extensive investigation into the relationship between patient perceptions and actual health outcomes and their longer term sustainability. More extensive statistical analysis and tests could then be carried out, revealing more about the interactions between the multiple factors that can affect patient perceptions of their health, including not only physiological indicators but the lifestyle practices that a programme like this aims to address.

Overall, this pilot study shows that holistic lifestyle-medicine health advice delivered via a group consultation approach leads to improvements in both physiological parameters and patient's perceived well-being. If these improvements are maintained, then it will lead to significant benefits, both for individuals, but also the health economy as there may be lower patient attendance in future, and health-related costs are reduced. The cost-effectiveness of healthy lifestyle improvement has been demonstrated in other studies elsewhere.[4,12] Our analysis suggests that this approach could be similarly cost-effective, with a relatively low-cost intervention resulting in significant QALYs gained and reduced future healthcare burden. These initial results support further investigation on a larger scale, with longer follow-up to allow further assessment of the cost-effectiveness.

Despite the inability to follow-up the longer term outcomes (due to the coronavirus pandemic restrictions), the results of this pilot study are very encouraging in terms of the potential for both health improvement and the related health psychology. A more extensive programme would provide opportunity to learn more about the relationships between patient perceptions and their actual health outcomes. A larger study would also enable longer term follow-up to assess the sustainability of changes made. For future iterations of this programme, consideration will have to be given to the current limitations on delivering care following the global pandemic. One possibility could be the use of technology to deliver sessions remotely, via virtual group consultations, which in itself has both benefits and drawbacks.

5 | CONCLUSION

This pilot project demonstrated improvements in the patients' perceived health and well-being, along with reductions in weight, and reduced problems with mood and pain. The participants engaged well with the course, with very positive feedback about the course itself,

and reported high levels of improved motivation and confidence. This suggests that lifestyle health advice delivered in a group setting with a holistic approach looking at all aspects of lifestyle medicine empowers patients to make positive lifestyle changes. Having a GP-led overarching approach enables holistic formulation of individualised action plans which take into account the complexity of each patient's needs, resulting in positive changes led by the patient that, in turn, lead to significant improvements in well-being. Our analysis shows that delivery of care in this way is cost-effective. The positive findings from this pilot-scale study support investment in a larger study to further develop and explore delivery of lifestyle medicine intervention in this way.

APPENDIX A: REGRESSION ANALYSIS

Relationship between patient health perceptions and weight

An equation of the following form was estimated as follows:

$$\Delta OH_i = \beta \Delta W\%_i + u_i,$$

Where ΔOH_i is the change in EQ VAS score for overall health of patient i, $\Delta W\%_i$ is the percentage change in the patient's weight, u_i is an error term, and $i = 1, \ldots, 11$.

A constant term was excluded on the assumption that patient perceptions of their health would not otherwise change over the 6-week period of the programme (except for random variations). Simple ordinary least squares (OLS) regression was used to estimate the coefficient β. In addition, a second equation of the same form was estimated in which $\Delta BMI\%_i$, the percentage change in the patient's BMI, was used instead as the independent variable. The results for both equations are set out in Table 7.

The coefficient of the percentage change in weight is significant at the 5% level (since $|t| > 2.228$). Similar results were obtained when the change in BMI was used instead as the independent variable. This is to be expected as weight is the numerator in the calculation of BMI, making the two variables $\Delta W\%_i$ and $\Delta BMI\%_i$ highly collinear ($R = 0.95$).

Both equations were re-estimated with the addition of dummy variables to allow for the effect of demographic factors. Variables for gender, age and marital status were tested individually in separate regressions, but none were found to be significant. There was virtually no variation in ethnicity in the sample.

Relationships between confidence, motivation and health perceptions

An equation of the following form was estimated as follows:

$$\Delta CON_i = \beta_1 \Delta OH_i + u_i,$$

where ΔCON_i is the change in the patient's score for confidence about making lifestyle changes and the other variables are as described in the previous section. In addition, two further equations of the same form were estimated using ΔMOT_i and ΔIMP_i instead as the dependent variable; the former being the change in the patient's score for motivation to make lifestyle changes and the latter being the change in the patient's score for the importance of making such changes. The coefficients of ΔOH_i in each of the three equations (viz. β_1, β_2 and β_3, respectively) were estimated using simple OLS and results are summarised in Table 8.

The table shows that the estimated coefficients of the change in overall health in the first two equations (β_1 and β_2) were both significant. The estimated coefficient in the third equation (β_3) was not significant, as would be expected because there was no significant difference between the means of the patients' importance scores.

The three equations were re-estimated including dummy variables as before, but again none were significant.

Further regression results were obtained using the percentage change in weight ($\Delta W\%_i$) instead as the independent variable in each

TABLE 7 OLS estimates of relationship between patient health perceptions, weight and BMI

			95% Confidence interval		Significance test		
Independent variable	Coefficient	SE	Lower	Upper	*t*-statistic	*P*-value	R^2
$\Delta W\%_i$	−5.403	2.402	−10.755	−0.051	−2.249	0.0482	0.336
$\Delta BMI\%_i$	−6.490	2.674	−12.449	−0.531	−2.427	0.0356	0.371

SE = standard error.

TABLE 8 OLS estimates of relationships between confidence, motivation, importance and health perceptions

			95% Confidence interval		Significance test[a]		
Dependent variable	Coefficient of ΔOH_i	SE	Lower	Upper	*t*-statistic	*P*-value	R^2
ΔCON_i	0.071	0.026	0.014	0.128	2.757	0.0202	0.432
ΔMOT_i	0.091	0.021	0.045	0.137	4.398	0.0013	0.659
ΔIMP_i	0.005	0.011	−0.019	0.029	0.491	0.6338 (NS)	0.024

[a]NS = not significant at the 5% level ($|t| < 2.228$, ie P-value > 0.05).
SE = standard error.

equation because this factor appears to have a significant effect on patients' perceptions of overall health. However, no significant results were obtained. This might be expected because the results in the previous section show that weight is unlikely to be the only factor affecting patients' health perceptions. The percentage change in weight was also not found to be significant when included as an additional independent variable in each of the three equations.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Do interactions between patients' psychological distress and adherence to dietary recommendation predict glycemic control among persons with type 2 diabetes in Ghana?

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Abstract

Introduction: Psychological distress is a pervasive mental condition among persons with chronic noncommunicable diseases.

Aim: To examine whether interactions between patients' psychological distress and adherence to dietary recommendations predict glycemic controls among persons with type 2 diabetes mellitus in Ghana.

Methods: Facility-based cross-sectional study involving 530 persons with type 2 diabetes mellitus was conducted between October 2018 and September 2019. Six health facilities were randomly selected and normal-weight persons with type 2 diabetes mellitus (T2DM) at baseline consecutively recruited from patients' registers. Structured questionnaires were used to collect sociodemographic data. Glycemic control was the main outcome variable, and was determined using HbA1c%. Statistical Package for Social Sciences version 22 was used in data analysis.

Results: Systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), total cholesterol, and fasting blood sugar were statistically significant for glycemic control (HbA1c%) (p-value < 0.05). After adjusting for confounding variables, low adherence and moderate adherence to dietary recommendations were independently significant for poor glycemic control (high HbA1c%). Interaction between low psychological distress and low adherence to dietary recommendations was statistically significant for poor glycemic control (high HbA1c%). Interaction between low psychological distress and moderate adherence to dietary recommendations was also statistically significant for poor glycemic control (high HbA1c%), whereas interaction between moderate psychological distress and high adherence to dietary recommendations was statistically significant for poor glycemic control (high HbA1c%).

Conclusion: Interaction between psychological distress and adherence to dietary recommendations can influence glycemic controls among persons with T2DM.

KEYWORDS
adherence, dietary recommendations, Ghana, glycemic control, psychological distress, type 2 diabetes

1 | INTRODUCTION

Psychological distress (PD) is an unpleasant or emotional feeling that affects functional capacity of individuals, but is often overlooked or gone unnoticed by healthcare workers. PD interferes with activities of daily living[1,2] and easily results in negative views of one's self, others, and the environment around them. The feeling of sadness, anxiety, distraction, and symptoms of mental illness are major manifestations of PD; however, the subjective severity of these manifestations depends on the situations and how the individuals perceive them.[3] Adverse health and social consequences such as chronic disease episodes, loss of home and livelihood, and death of family members or love ones are major determinants of PD.[4]

Diabetes mellitus (DM) is one of the adverse health conditions that can precipitates PD,[5] which in turn affects diabetes management (glycemic control and self-care practices) among patients.[6] DM is a threat to global health and national development, due to its longstanding complications and difficulties in management. Although the advent of sophisticated technologies and machines in the 21st century has made detections and diagnoses of DM much easier,[7] PD among persons with DM still goes unnoticed or undiagnosed and thus contributes significant treatment nonadherence.[8] These problems are known to dramatically drain states and individual resources, and thus bestow untoward economic hardships on the entire population.[9,10] The aim of treatment protocols in diabetes management is to reduce microvascular (i.e., eye and kidney disease) disease risk through control of glycemia and blood pressure and macrovascular (i.e., coronary, cerebrovascular, and peripheral vascular) disease risk through control of lipids and hypertension smoking.[11] However, when PD among patients is unidentified and untreated, it offset the benefits of diabetes treatment protocols and thus increased patients' risk of complications.[12] PD is a major problem among persons with chronic noncommunicable diseases including DM globally and in Ghana.[13] In Amankwah-Poku et al.'s study, it is reported that diabetes distress correlated negatively with dietary and exercise regimen.[14] In another study among community dwellers with DM in Ghana, the incidence of psychological distress was reported to be increased among those living alone,[15] thus indicating how pervasive psychological distress is among persons with DM in Ghana. PD is a major comorbid condition that increased patients' vulnerability to complication[16] as result of nonadherence to treatment protocols.

Dietary recommendations are important components in diabetes management that focus on counseling clients to follow healthy dietary pattern to manage glycemia and prevent diabetes-related complications. Patients put on dietary recommendations for diabetes management are often counseled to stick to regular eating time/pattern relative to medication intakes[17,18]; they are often advised to eat more of fruits and vegetables, whole grains, legumes, low-fat dairy foods, heart-healthy fish, and lean meat and avoid diets high in saturated fats, trans fat, cholesterol, and sodium.[17,18] These dietary recommendations are often made in line with patients' socioeconomic status and cultural backgrounds for proper adherence.[19,20] Although dietary recommendations are proven to be effective in controlling diabetes and related complications, due to the effects of PD among DM patients in Ghana, very little is known about how adherence to dietary recommendations influences treatment outcomes among DM patients. When patients with DM also have psychological distress, their correct judgments in making proper decision to select healthy foods and follow dietary recommendations are compromised. Despite this, little is known about how psychological distress interacts with dietary recommendations to influence treatment outcomes (glycemic control) among persons with T2DM in Ghana. In view of this, our study hypothesized that psychological distress can interact with dietary recommendations to influence glycemic control among persons with T2DM. In order to evaluate this hypothesis, we aimed to examine whether interaction between patients' psychological distress and adherence to dietary recommendation predicts glycemic controls among persons living with T2DM in Ghana.

2 | METHODS

2.1 | Study design

Facility-based cross-sectional study was conducted among 530 normal-weight (body mass index [BMI] 18.5–24.9 kg/m^2) persons with T2DM in Brong Ahafo Region (BAR), Ghana. In this study, individuals 18 years and above, diagnosed with T2DM by physicians using the American Diabetes Association (ADA) Diagnostic and Classification Guideline,[21] and were counseled to follow feeding recommendations for at least 3 months were recruited. Individuals 70 years and above who could not answer interview questions, were mentally incapacitated, severely ill, pregnant, and lactating women were excluded.

2.2 | Procedure

Simple random sampling was used to select six hospitals in BAR. The eligible participants for this study were consecutively recruited into the study using patients' registration numbers from patients' register. Before participants were recruited, the purpose of the study was explained to them in their local dialect (twi) and their consents were then sought for participation. After patients consented to participate, trained research assistants (first degree in nutrition and dietetics, and

psychology graduating) on their national service in hospitals administered the questionnaires to patients. Each research assistant spent on average 15 min to complete a set of questionnaire per participant. The total duration of the data collection in the six hospitals was 11 months. Kessler 10-item (K-10) Psychological Distress Scale, Perceived Dietary Adherence Questionnaire (PDAQ) for persons living with T2DM, WHO 10-item Alcohol Use Disorder Identification Scale (AUDITs-10), Fagerström Test for Nicotine Dependency, and structured questionnaires were used to extract data from participants.

2.3 | Ethical approval

Ethical approval was obtained from Ghana Health Service Ethics Review Committee (GHS-ERC008/08/18) and Tehran University of Medical Sciences Ethics Review board (IR.TUMS.VCR.REC.1397.409). All participants were requested to sign a written informed consent before participating in the study.

2.4 | Assessing patients demographic characteristics, anthropometrics, and clinical parameters

Age, diabetes duration, medication intakes, and clinical and other demographic characteristics were assessed using structured questionnaires. Weight (kg) and height (m) were measured and recorded to the nearest 0.5 kg and 0.5 m using adult weighing scale and stadiometer, respectively. Weight and height measurements were done by asking participants to wear light clothes without shoes and be in standing position. BMI was calculated by dividing the body weight in kilograms by the square of height in meters (kg/m^2). Systolic and diastolic blood pressures were measured using manual sphygmomanometer and stethoscope, and the reading recoded to the nearest 0.5 mm Hg, after participants were asked to relax for 5 or more minutes.

2.5 | Assessing participants' glycated hemoglobin (HbA1c%)

Participants' glycemic control (HbA1c%) was estimated using laboratory procedures (turbidimetric inhibition immunoassay method) as described in literature.[22] The HbA1c% test results obtained from this laboratory test were categorized as good glycemic control (HbA1c% <6.0%), moderate glycemic control (HbA1c% = 6.0%–6.4%), and poor glycemic control (HbA1c% ≥ 6.5%).

2.6 | Assessing patients psychological distress

Patients' psychological distress was assessed using Kessler Psychological Distress Scale (K-10). This scale has five Likert's response, ranging from *none of the time* to *all of the time*.[23] Patients who responded *none of the time* to all items in the Likert's scales were said to have no psychological distress. Those who reported *a little of the time* were said to have low psychological distress, whereas those who reported *some of the times* were said to have moderate psychological distress. Finally, patients who reported *most of the time* and *all of the time* to all items in the Likert's scale questionnaires were said to have high psychological distress. The items under the K-10 were summed up to form global score and represented patients' total psychological distress. Patients' total psychological distress on the global score was 40. Based on this, the degree of PD was categorized. Patients who scored a sum of zero (0) points on the scale were said to have "no" psychological distress, those who scored a sum ranging 1 to 9 were said to have low psychological distress, and those who scored a sum ranging from 10 to 19 points were said to have moderate psychological distress. Finally, participants who scored a sum of points ranging from 20 to 40 were said to have high psychological distress. These questionnaires were pretested among 20 participants (Cronbach's alpha = 0.65).

2.7 | Assessing participants' alcohol intake

AUDITs-10 was also used to assess patients' alcohol intake level. Patients were asked to respond to the 10 points in AUDITs scale, ranging from *How often do you have drink containing Alcohol?* to *Has a relative, friend, doctor, or other health care worker ever been concerned about your drinking and suggested that you cut it down*? The responses to these questions were also on a Likert's scale of 1 = (*Never*), 2 = (*two to four times a month*) 3 = (*two to three times a week*), and 4 = (*four or more times a week*). Per our category on the scale based on patients score, patients who report *Never* to all the item on the scale were said to have no alcohol intake history, those who reported intake of *two to four times a month* were said to have low alcohol intake history, whereas those reported intake of *four or more times a week* were said to have high alcohol intake history. The results obtained from patients were also summed up to represent patients' alcohol intake status. These questionnaires were also pretested among 20 participants (Cronbach's alpha = 0.55).

2.8 | Assessing participants' smoking status

Fagerström six-item Test for Nicotine Dependency was also used to assess participants smocking status. Participants were asked to respond to six items in the Fagerström Test for Nicotine Dependency, ranging from *How soon after you wake up from bed do you smoke your first cigarette?* to *Do you smoke even if you are so ill that you are in bed most of the day?* with responses ranging from 0 to 3. Again these responses were summed up to 10. Participants who reported 0 were said to have no smoking history. Those who reported 1 were said to have low smoking history and those who reported 2 and above were said to have high smoking history. These questionnaires were also pretested among 20 participants (Cronbach's alpha = 0.55).

2.9 | Assessing patients adherence to dietary recommendations

PDAQ for persons living with T2DM were used to assess adherence to dietary recommendations.[24] These questionnaires are based on nine-item and 7-point Likert's scale designed to elicit information about adherence to dietary recommendations, among persons with DM. These Likert's scale questionnaires have points ranging from 0 to 7. Participants who scored 0 point to any question on the scale were said to have nonadherence to that question, and those who scored 7 point to any question on the scale were said to have highest adherence to those items on the scale. The nine items in the questionnaires were also summed up to form global score and represented patients' total adherence to dietary recommendations. Patients' total adherence score was 63. Again this score was also categorized into "low," "moderate," and "high" adherence. Based on these, patients who scored a sum of zero (0) points on the scale were said to have no adherence. Those who scored a sum of "1–42" were said to have moderate adherence and those who scored a sum of "43–63" points were said to have high adherence to dietary recommendations. These questionnaires were also pretested among 20 participants (Cronbach's alpha = 0.95).

2.10 | Statistical analysis

IBM SPSS version 22.0 (SPSS, Chicago, IL, USA) was used to ran all statistical analysis. Normal distributions of data were checked using Kolmogorov–Smirnov test. Descriptive statistics were used to describe patients' demographic characteristics, and one-way ANOVA with post hoc Bonferroni multiple comparison test was used to demonstrate significant mean differences between groups (low, moderate, and high adherence to dietary recommendations). Polynomial logistic regression models were used to assess the association of psychological distress, dietary recommendation, and their interaction for glycemic control. The significance for all variables was set at 0.05 alpha levels.

3 | RESULTS

Patients' demographic characteristics, anthropometry, and clinical parameters are shown in Table 1. Mean (SD) for Age (years), BMI (kg/m^2), and fasting blood sugar (FBS) (mmol/L) is 58.10 (9.70), 23.14 (2.92), and 10.05 (4.55), respectively. Mean (SD) for total adherence to dietary recommendations, total psychological distress, and glycemic control (HbA1c %) is 32.56 (9.61), 5.33 (5.21), and 8.13 (3.2), respectively. Majority of participants (70.9%) were females, married (64.2%), and lived in small towns (76.2%). More than 38% of participants had no formal education, 1.9% have polytechnic education, 2.5% have university education, and the rest have education from primary to senior high school.

Comparison of mean differences of participants' demographic characteristics, anthropometry, and clinical parameters for adherence to dietary recommendations are shown in Table 2. There were significant mean differences in BMI (kg/m^2), total cholesterol, HbA1c (%), and FBS (mmol/L) (p-value < 0.05) for low, moderate, and high adherence to dietary recommendations.

The association of psychological distress, adherence to dietary recommendations, and their interaction for glycemic control are shown in Table 3. After adjusting for confounding factors (age, education level, diabetes duration, medications, alcohol intake, and smoking), there was no statistically significant association of psychological distress for glycemic control. However, moderate adherence to dietary recommendations was statistically significant for moderate glycemic control (moderate HbA1c %) (adjusted odd ratio [AOR] = 1.79; 95% confidence interval [CI], 1.03–3.13) and poor glycemic control (high HbA1c %) (AOR = 2.78; 95% CI, 3.98–10.19). Low adherence to dietary recommendations was also statistically significant for moderate glycemic control (moderate HbA1c %) (AOR = 1.79; 95% CI, 1.03–3.13) and poor glycemic control (high HbA1c %) (AOR = 2.78; 95% CI, 3.98–10.19), whereas interactions between low psychological distress and low adherence to dietary recommendations were statistically significant for moderate glycemic control (moderate HbA1c %) (AOR = 1.08; 95% CI, 1.52–10.96) and poor glycemic control (high HbA1c %) (AOR = 3.68; 95% CI, 4.64–34.61). Again interactions between low psychological distress and moderate adherence to dietary recommendation were statistically significant for poor glycemic control (high HbA1c %) (AOR = 1.69; 95% CI, 2.79–17.51), whereas interaction between low psychological distress and high adherence to dietary recommendations was statistically significant for moderate glycemic control (moderate HbA1c %) (AOR = 1.15; 95% CI, 1.23–9.68) and poor glycemic control (HbA1c %) (AOR = 1.61; 95% CI, 3.73–24.96). Furthermore, interaction between moderate psychological distress and low adherence to dietary recommendations was statistically significant for moderate glycemic control (moderate HbA1c %) (AOR = 1.22; 95% CI, 1.63–9.45) and poor glycemic control (high HbA1c %) (AOR = 1.24; 95% CI, 1.57–11.41), whereas interactions between moderate psychological distress and high adherence to dietary recommendations were statistically significant for moderate glycemic control (moderate HbA1c %) (AOR = 1.88; 95% CI, 1.89–12.60) and poor glycemic control (high HbA1c %) (AOR = 1.01; 95% CI, 1.72–14.57). Finally, interaction between high psychological and low adherence to dietary recommendations was statistically significant for moderate glycemic control (moderate HbA1c %) (AOR = 2.06; 95% CI, 1.09–5.97).

4 | DISCUSSION

T2DM is a pervasive medical condition that precipitates psychological distress, which when not carefully managed can act independently or in tandem with treatment protocols to compromise treatment outcomes. In this facility-based cross-sectional study, we evaluated how psychological distress can independently, or interact with dietary recommendations to, influence glycemic control among person with T2DM in Ghana. Our results found no statistically significant association of psychological distress for glycemic control. However, we found that moderate and low adherence to dietary recommendations

TABLE 1 Participants demographic characteristics, anthropometry, and clinical parameters

Variable	Means (SD)	Number (%)
Age (years)	58.10 (9.70)	
Wight (Kg)	61.70 (9.30)	
Height (m)	1.63 (0.09)	
BMI (kg/m^2)	23.14 (2.92)	
HbA1c	8.13 (3.20)	
FBS	10.05 (4.55)	
Total cholesterol	7.19 (3.49)	
HDL-C	1.74 (0.90)	
LDL-C	5.15 (3.42)	
Triglycerides	4.64 (14.14)	
Systolic blood pressure (mm Hg)	135.67 (7.79)	
Diastolic blood pressure (mm Hg)	77.79 (12.79)	
Diabetes duration (years)	4.90 (5.40)	
Duration lived with diabetes (years)	4.90 (5.40)	
Total adherence to dietary recommendation	52.82 (0.57)	
Psychological distress	5.33 (5.21)	
Sex		
Male		154(29.1)
Female		376(70.9)
Marital status		
Married		340(64.2)
Single		20(3.8)
Widow		107(20.2)
Divorce		63(11.9)
Place of residence		
Village		39(7.4)
Town		404(76.2)
City		87(16.4)
Educational Level		
No education		202(38.1)
Primary		85(16.0)
Junior high		132(24.9)
Senior high		67(12.6)
Training college		21(4.0)
Polytechnic		10(1.9)
University		13(2.5)

Abbreviations: BP, blood pressure; HbA1c, glycosylated hemoglobin; FBS, fasting blood sugar; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

were both statistically significant for moderate glycemic control (moderate HbA1c %) and poor glycemic control (high HbA1c %). Again we found that interaction between low psychological distress and low adherence to dietary recommendations was statistically significant for moderate glycemic control (moderate HbA1c%) and poor glycemic control (high HbA1c%), whereas interaction between low psychological distress and moderate adherence to dietary recommendations was statistically significant for poor glycemic control (high HbA1c %). Furthermore, we found that interactions between low psychological distress and high adherence to dietary recommendations were statistically significant for moderate glycemic control (moderate HbA1c %) and poor glycemic control (high HbA1c%), whereas interactions between moderate psychological distress and low adherence to dietary recommendations were statistically significant for moderate

TABLE 2 Comparison of means differences of participants' demographic characteristics, anthropometry, and clinical parameters in adherence to dietary recommendation

	Adherence							
	Low		Moderate		High			
Variable	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*F*-statistics (df1,df2)[a]	*p*-Value[b]
Age (years)	181	58.63 (10.06)	175	57.11 (10.01)	174	58.40 (8.78)	1.268 (2,527)	0.282
BMI (kg/m^2)	181	22.58 (2.81)	175	23.47 (2.96)	174	23.39 (2.92)	5.235 (2,527)	0.006
Systolic blood pressure (mm Hg)	181	134.31 (21.68)	175	137.41 (19.59)	174	135.32 (19.96)	1.057 (2,527)	0.348
Diastolic blood pressure (mm Hg)	181	77.32 (12.36)	175	78.87 (12.44)	174	77.19 (13.57)	0.935 (2,527)	0.393
Diabetes duration (yeas)	181	4.48 (2.98)	175	4.75 (2.99)	174	5.03 (3.07)	1.493 (2,527)	0.226
Total cholesterol (mg/dL)	181	6.88 (3.39)	175	6.36 (3.39)	174	7.97 (3.64)	5.754 (2,527)	0.003
HDL cholesterol (mg/dL)	181	1.81 (0.98)	175	1.71 (0.89)	174	1.69 (0.82)	0.985 (2,527)	0.374
LDL cholesterol (mg/dL)	181	5.43 (3.45)	175	5.08 (3.84)	174	4.94 (2.86)	0.993 (2,527)	0.371
Triglyceride (mg/dL)	181	4.11 (11.71)	175	5.42 (16.75)	174	4.39 (13.63)	0.417 (2,527)	0.659
HbA1c (%)	181	9.58 (3.79)	175	7.69 (2.51)	174	7.07 (2.61)	32.890 (2,527)	0.0001
Fasting blood sugar (mmol/L)	181	11.59 (5.28)	175	9.69 (4.14)	174	8.81 (3.60)	18.563 (2,527)	0.0001

[a]One-way ANOVA.
[b]Post hoc analysis with Bonferroni correction that shows significant mean differences in BMI for low adherence and other adherence to dietary recommendation (*p*-value = 0.006), total cholesterol for low adherence and other adherence to dietary recommendation (*p*-value = 0.003), and fasting blood sugar for low adherence and other adherence to dietary recommendation (*p*-value = 0.0001).

TABLE 3 Association of psychological distress, adherence to feeding recommendation, and their interactions for glycemic control

Variable		Moderate HbA1c (%) COR (95% CI)	*p*-Value	High HbA1c (%) COR (95% CI)	*p*-Value	Moderate HbA1c (%) AOR (95% CI)	*p*-Value	High HbA1c (%) AOR (95% CI)	*p*-Value
High psychological distress	Ref.	1		1		1		1	
Mod.Pych.		0.87 (0.52–1.47)	0.604	0.84 (0.48–1.44)	0.516	0.88 (0.51–1.49)	0.625	0.88 (0.50–1.54)	0.650
Low psychological		1.46 (0.86–2.48)	0.165	1.64 (0.95–2.85)	0.077	1.49 (0.86–2.57)	0.156	1.59 (0.89–2.83)	0.115
High adherence	Ref.	1		1		1		1	
Moderate adherence		1.81 (1.05–3.11)	0.033	1.03 (1.16–3.54)	0.013	1.08 (1.25–3.43)	0.004	1.08 (1.17–3.71)	0.013
Low adherence		1.94 (1.19–3.17)	0.008	5.61 (3.24–9.69)	0.001	1.79 (1.03–3.13)	0.040	2.78 (3.98–10.19)	0.001
High Pych × High Adherence.	Ref.	1		1		1		1	
Low Pych × Low Adherence		3.81 (1.45–10.03)	0.007	1.77 (4.45–31.15)	0.0001	1.08 (1.52–10.96)	0.005	3.68 (4.64–34.61)	0.001
Low Pych × Mod. Adherence		3.63 (1.54–8.57)	0.003	1.35 (1.68–11.28)	0.002	1.98 (0.80–4.91)	0.142	1.69 (2.79–17.51)	0.001
Low Pych × High Adherence		2.47 (1.07–5.67)	0.034	2.41 (0.93–6.27)	0.070	1.15 (1.23–9.68)	0.019	1.61 (3.73–24.96)	0.001
Mod.Pych × Low Adherence		1.77 (0.81–4.81)	0.134	1.29 (2.58–15.33)	0.0001	1.22 (1.63–9.45)	0.002	1.24 (1.57–11.41)	0.004
Mod.Pych × Mod. Adherence		2.20 (0.98–4.93)	0.055	1.72 (0.66–4.48)	0.269	2.40 (1.05–5.47)	0.038	1.87 (0.70–4.99)	0.213
Mod. Pych × High Adherence		1.75 (0.74–4.14)	0.205	1.54 (0.56–4.26)	0.404	1.88 (1.89–12.60)	0.001	1.01 (1.72–14.57)	0.003
High Pych × Low Adherence		1.15 (1.26–9.47)	0.016	2.51 (3.07–23.59)	0.0001	2.06 (1.09–5.97)	0.030	2.40 (0.90–6.44)	0.081
High Pych × Mod Adherence		2.32 (1.71–10.93)	0.002	1.32 (1.53–12.22)	0.006	1.82 (0.75–4.40)	0.185	1.72 (0.61–4.90)	0.306

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COR: crude odd ratio

glycemic control (moderate HbA1c%) and poor glycemic control (high HbA1c %).

Studies show that significant associations exist between adherence to dietary recommendations and blood glucose levels among persons with diabetes.[25,26] PD is common comorbid condition that affects persons with diabetes.[27] When this condition exists, persons with diabetes may not have clear conscience to make decisions for foods selection and consumption to effectively manage glycemia. This phenomenon could therefore adversely affect patients' long-term glycemic control. The effects of psychological distress in blood glucose control among persons with diabetes have been well researched in many epidemiological studies.[28] In a study among persons with T2DM in Ghana, Amankwah-Poku et al. noted that psychosocial distress can act as a barrier to diabetes self-care management and thus compromise diabetes control.[14] Yet, healthcare workers in Ghana mainly focus on the medical aspect of diabetes to the neglect of psychosocial care.[14] These findings are in consonance with our study; it is observed that patients' optimum adherence to dietary recommendations is an important aspect in controlling blood glucose for diabetes management.[29] However, when psychological distress exists, optimum adherence to dietary recommendations is compromised and thus causes poor or suboptimum glycemic control. In our study, we found that although psychological distress alone did not show any significant association for glycemic control, when this variable interacted with adherence to dietary recommendations, they clearly showed significant associations for glycemic controls. These findings therefore indicate that despite patients' optimum adherence to dietary recommendations is important in controlling glycemia,[30] the present condition of psychological distress could compromise optimum adherence. These findings further give clue that as dieticians seek to help persons with diabetes in maintaining and improving glycemic control, they should bear in mind the effects of psychological distress and treat it.

In our study, we also observed that interaction between low psychological distress and high adherence to dietary recommendations was significant for moderate and poor glycemic control (moderate HbA1c% and high HbA1c %), whereas interaction between low psychological distress and moderate adherence to dietary recommendations was statistically significant for poor glycemic control (high HbA1c %). These findings again shed light on the fact that controlling psychological distress in human life is important in disease management. PD is a pervasive condition in human health; human physical health and well-being are functions of psychological wellness.[31] If psychological wellness is compromised, functional capacity could also be compromised. In our day to day interactions, we make choices and adjustments to cope with circumstances that come our ways. However, when PD is present, our quest to make choices and adjustments could be compromised, and thus adversely affect our behaviors. As shown in our study, although dietary recommendations independently predicted glycemic control, the presence of unmanaged psychological distress (low PD) in the midst of adherence to dietary recommendations clearly compromised glycemic control. Kalra et al. noted that addressing psychosocial distress among persons with diabetes could overcome barriers associated with adherence to treatment and self-care practices,[27] which is consistent with our findings.

In our study, we again observed that interaction between low psychological distress and low adherence to dietary recommendations was statistically significant for moderate and poor glycemic control, whereas interaction between low psychological distress and moderate adherence to dietary recommendations was statistically significant for poor glycemic control (high HbA1c %). These results again show us that although dietary recommendations are seen as magic bullets in achieving long-term glycemic control, the presence of PD in any form (low, moderate, or high) could counter the positive effect of dietary recommendations. Indelicato et al. noted that psychological distress was closely associated with poorer glycemic control.[32] Although Indelicato et al. did not investigate the interaction between psychological distress and adherence to dietary recommendations for glycemic control, their finding supported our results, because they noted that psychological disturbances are strong factors that adversely influence treatment outcomes. Most persons with chronic noncommunicable diseases often have different forms of psychological problem.[33] If these problems are left unidentified and unmanaged, they pose overwhelming consequences to human survival. As we seek to give care to persons with diabetes and other chronic noncommunicable diseases, it is important that we take cognizant look at how different aspects of the disease dynamics could precipitate psychological distress, which could subsequently affect adherence to treatment protocols.

In our study, we again found that interaction between moderate psychological distress and high adherence to dietary recommendations was statistically significant for moderate and poor glycemic control, whereas interaction between high psychological distress and low adherence to dietary recommendations was statistically significant for moderate glycemic control.

5 | STUDY LIMITATIONS

Although we found significant associations of dietary recommendations, and their interactions with psychological distress for glycemic control, we cannot strongly conclude on that based on our results by saying that causal associations exist for psychological distress, adherence to dietary recommendations, and their interactions for glycemic controls among person with T2DM. This is because of possible biases and methodological flaws. Our study employed facility-based cross-sectional study. Because cross-sectional study cannot detect causal associations of study variables, we suggest that subsequent studies on this subject should consider adopting stronger study design such as cohort study or clinical trial to investigate this matter. We also recruited relatively small sample size (530), which limits the power of the study; in this regard, we again recommend that subsequent studies on this matter should consider quite larger sample size to improve the power of the study. Also some of our data collection tools (Kessler [K-10], AUDITs-10 scale, and Fagerström Test for Nicotine Dependency) have relatively low reliability (Cronbach's alpha < 0.70). Despite these methodological and study tool reliability flaws, the strength of our

study is that it is the first of its kind in literature that explored how psychological distress can interact with adherence to dietary recommendations for glycemic control among persons with diabetes mellitus.

5.1 | Policy implication

The policy direction for our study therefore is that patients with diabetes mellitus reporting to health facilities should be carefully screened by qualified healthcare workers to identify and manage psychosocial distress in patients before initiating diabetes-specific treatment protocol. Healthcare workers can manage psychological distress in patients by adopting psychotherapy approach such as problem-solving approach to help patients manage psychological distress effectively.

6 | CONCLUSION

In our study, we found that psychological distress was not independently significant for glycemic control. However, adherence to dietary recommendations was significant for glycemic control and interaction between psychological distress and adherence to dietary recommendation was also statistically significant for glycemic controls. These findings therefore caution healthcare professionals caring for persons with DM to be mindful of the impact of psychological distress and treat them for optimum adherence to treatment protocols.

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AUTHOR CONTRIBUTIONS

BDD collected and analyzed the data and wrote the manuscript. AA obtained ethical clearance in Ghana for this study, supervised the data collection, and proofread the final version of the manuscript before submission. YM supervised the data analysis and proofread the final version before submission. SE proofread the final version of the manuscript before submission. AD acquired funding for the study, supervised the data collection process, and proofread the final version of the manuscript before submission. MK supervised, coordinated the study, took part in the data collection took p art in the data analysis and wrote the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Medical specialties and life expectancy: An analysis of doctors' obituaries 1997–2019

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Abstract

Background: Previous studies have found emergency medicine physicians have a reduced life expectancy compared to other doctors, using small subsets of data from the obituary section of the British Medical Journal. Technological advances now allow the entire catalogue of obituaries to be interrogated, which allows exploration of the relationship between medical specialty, age at death and cause of death in doctors.

Methods: Publicly available electronic records were obtained by web scraping and analysed with natural language processing algorithms. Obituaries published in the British Medical Journal between January 1997 and August 2019 were scraped and analysed for differences in age and cause of death and also relative survival analysis compared to the general U.K. population.

Results: Data were extracted from 8156 obituaries. The specialties with the oldest average age at death were general practitioners (80.3, *SD* = 12.5, *n* = 2508), surgeons (79.9, *SD* = 13.6, *n* = 853) and pathologists (79.8, *SD* = 13.8, *n* = 394). The specialties with the youngest average age at death were emergency physicians (58.7, SD = 23.6, *n* = 43), anaesthetists (75.5, *SD* = 16.1, *n* = 473) and radiologists (75.8, *SD* = 14.5, *n* = 172). Cancer was the most common cause of death and did not differ by specialty. Doctors on average have an older age at death than the general U.K. population.

Conclusions: A doctor's specialty has a significant association with their age at death, with general practitioners living the longest and emergency physicians the shortest, with proportionately more accidental deaths. Likely due to its recency as a separate specialty, the emergency physician group is the smallest, which may censor and falsely reduce this group's age at death. The observed increased life expectancy and the reduced cardiovascular disease in this cohort may be associated with lifestyle and socioeconomic factors.

KEYWORDS
epidemiology, life expectancy, life style

1 | INTRODUCTION

Historically, doctors have been involved in epidemiology and public health not only as researchers but also participants.[1] As early as 1949, it was noted that the commonest causes of death amongst doctors were different from the general population.[2] However, there is little contemporary information regarding the life expectancy and cause of death of doctors in the United Kingdom.

The British Medical Journal's obituary column details the lives and deaths of doctors with a connection to the United Kingdom on a weekly basis, with its electronic archives containing over 20 years' worth of obituaries. This is a free service and deceased doctors need not be a member of the BMA or live or work in the United Kingdom. No obituaries are refused, and every submitted obituary is published online. Thus, the British Medical Journal (BMJ) website holds a collection of memories of doctors from a range of backgrounds. Within these memories is a wealth of epidemiological information which, although difficult to extract, provides interesting data. Subsets of these data have been analysed previously. Wright et al. used a sample of 572 obituaries, finding that doctors born in the Indian subcontinent die earlier than those born in the United Kingdom.[3] Patel et al. used 3342 obituaries to describe that primary care doctors can expect to live 20 years longer than an emergency medicine (EM) doctor.[4]

Governments, institutions and companies are increasingly storing data online, allowing researchers easy access to collected data. Some websites facilitate access to this with an Application Program Interface (API); however, most do not. Web scraping is a specialist programming technique used in a variety of industries to automatically collect data from websites in bulk. Once bulk data are obtained, Natural Language Processing (NLP) can be applied to extract data variables. NLP refers to the method by which machines can be instructed on how to detect target variables stored in continuous prose rather than in a machine-friendly delimited format. Together, web scraping and natural language processing allow the procurement and interrogation of cumbersome online datasets.

This study aims to apply web scraping and natural language processing techniques to the BMJ obituary archives to produce a descriptive analysis of the data held in this large, publicly available dataset.

2 | METHODS

2.1 | Design and setting

This retrospective analysis of publicly available data was performed with the permission of the BMJ. Obituary pages were digitally 'scraped' on 7 August 2019 using an algorithm written in the Python (version 3.6) computing language.[5]

2.2 | Participants

Obituaries have been published by the BMJ since 1852. Entries are submitted by friends or family of the deceased within 1 year of the date of death. Smaller numbers of obituaries about prominent members of the medical community are commissioned by the BMJ. The majority are U.K.-based doctors; however, occasional international and non-clinical submissions are published. Since 1997, obituaries have been available in a machine-readable format (in hypertext markup language). Prior to this, they were only available in print or as pdf documents. All obituaries published on the BMJ website in machine readable form until 7 August 2019 were eligible for inclusion.

2.3 | Variables

Natural language processing was used to automatically extract variables from each obituary entry. Extracted variables were as follows: gender, date of birth, cause of death, specialty, professional memberships and year and place of qualification of the deceased. In order to analyse these variables, they were categorised: Cause of death was assigned according to the NHS atlas of risk which has 18 categories. Specialties were put into 10 groups according to royal colleges: physicians, surgeons, GPs, anaesthetists, paediatricians, EM, obstetricians and gynaecologists, pathologists, psychiatrists and ophthalmologists. If multiple specialties were present in a given record, the main specialty was assigned based on a hierarchical model. First, any specialty preceded by 'consultant' was considered the main specialty, in accordance with U.K. practice. Secondly, if no consultant specialties were present, then we assumed the last recorded specialty to be the main specialty.

A sample of 1% of the automatically extracted variables were checked by a clinician and error rates for both incorrect and missed assignments were recorded.

2.4 | Outcomes

The primary outcome measure was age at death. As the exact date of death was inconsistently recorded, conservative age at deaths was used by subtracting 1 year from difference between the year of publication and the year of birth, given consistent reporting of year of birth.

2.5 | Statistical analysis

Demographic data were calculated and compared according to specialty. Averages were calculated as means with standard deviation unless otherwise stated. Analysis of variance (ANOVA) was used for mean age at death and Tukey's Honest Significant Difference (HSD) test was used to determine which groups had increased or decreased mean ages. Sensitivity analysis using multiple linear regression allowed the effect of assigning one main specialty for doctors with multiple specialties over their careers to be tested.

To avoid the pitfalls of performing risk analysis without a denominator, non-parametric relative survival analysis was estimated using the 'relsurv' package in R.[6] Relative survival is defined as the ratio of the proportion of observed survivors in this cohort to the proportion of expected survivors in the general population. It is calculated by

TABLE 1 Completeness of automatic data extraction and manual check

Variable	Automatic extraction	False extraction	Missed extraction
Year of birth	8024/8156 (98.4%)	0/81 (0.0%)	0/81 (0.0%)
Year of publication	8156/8156 (100.0%)	0/81 (0.0%)	0/81 (0.0%)
Gender	8156/8156 (100.0%)	0/81 (0.0%)	0/81 (0.0%)
Year of qualification	7552/8156 (92.6%)	2/81 (2.5%)	2/81 (2.5%)
Specialty	7477/8156 (91.7%)	8/81 (9.9%)	2/81 (2.5%)
Cause of death	4345/8156 (53.3%)	9/81 (11.1%)	2/81 (2.5%)

Note: Completeness of automatic data extraction, and corresponding results from manual check of 1% of results. Details regarding cause of death were frequently omitted from obituaries. Automatic extraction refers to the proportion of cases where the algorithm assigned the variable. False extraction means that the automated process incorrectly assigned that variable. Missed extraction means that the variable was recorded in the obituary but was not extracted. Results are given as number/total (percentage).

dividing the percentage of the cohort who are still alive at the end of each period of time by the percentage of people in the U.K. general population of the same sex, age, and year of birth who are alive at the end of the same time period.[7] The U.K. death table data were used as the reference cohort as the obituary section is intended for doctors with a U.K. connection, though not all of the deceased will have lived in the United Kingdom. The relative survival analysis shows whether being a doctor is associated with a different life expectancy compared to the general population. This approach is more usually applied to cancer registries; however, in this case instead of date of diagnosis, date of qualification is used to mark the start of the exposure. This approach considers the population mortality hazard of the baseline population, in which doctors make up an insignificant proportion. The resulting difference in mortality can be associated with becoming a doctor. Within the 'relsurv' package the 'rs.surv' function, the 'Ederer 2' model was used due to its more conservative estimates and robustness over long time periods.[8]

3 | RESULTS

A total of 8156 BMJ obituaries were obtained from the BMJ website spanning more than 22 years between 1997 and 2019. In this period, there were 6395 obituary webpages, of which we collected data from 6310; 85 of the webpages were not available to read on the date of our analysis. Missing data may be due to obituaries omitting details or failure of automatic data extraction logic (see Table 1 for breakdown).

There were significant differences in the mean age at death amongst different specialties (see Table 2). In a linear regression model (ANOVA and subsequent Tukey test), emergency physicians have a significantly reduced mean age at death compared to all other specialties. Sensitivity analysis using multiple linear regression showed this relationship persisted for doctors who had multiple specialties ascribed to them but had worked in EM during their career ($n = 89$). This cohort are also shown as a separate column in Table 2. Further subgroup analysis used the country of qualification to show comparable trends with U.K. qualified doctors only.

Relative survival analysis (Figure 1A) shows that, compared to U.K. contemporaries born in the same year, this cohort has a survival advantage. This is evident 4 years after qualification with a tiny effect size (relative survival ratio 1.004 (95% confidence interval, 1.001–1.003)) but increases exponentially with time after qualification. This trend holds in all specialties (Figure 1B) except EM whose survival trend is below that of the reference population.

Cancer is the leading cause of death, causing 3191 of the 8156 (39.1%) deaths in this sample, and remains the leading cause regardless of sub-categorisation by specialty. The most common national cause of death, heart and circulatory disorders, is the second most common cause of death in all specialties, but EM for which it is non-transport accidents.

4 | DISCUSSION

There is a significant difference in age at death according to a doctor's specialty. Exposure to an emergency, anaesthetic, paediatric, radiology or psychiatry job is associated with earlier age at death, whereas pathology, surgery and GP were associated with an older age at death. The largest difference is seen in EM, with a younger mean age at death of 58.7 years and an increased proportion of accidental deaths than other specialties. The most common cause of death across all specialties according to the NHS risk atlas (cancer) differs from that of the general U.K. population (heart and circulatory disorders). On average, this cohort lives longer than the general population. Relative survival analysis demonstrates that this cohort shares the same risk as age- and sex-matched members of the U.K. population for the first 4 years of practice. Many years after qualification, there is a substantial survival advantage amongst all specialties aside from EM.

There are general lifestyle hazards associated with the profession relating to mental health and suicide, with suicide by self-poisoning and cutting more common than the general population.[9] Furthermore specialty-specific hazards include the burden of complaints, radiation exposure, exposure to harmful gases and shift patterns.[9–11] There is recent evidence that trainees in acute specialties, particularly EM, have very high rates of burnout.[12] The concerning risk of early death amongst EM doctors was first described a decade ago based on a much smaller subset of these data, containing only 17 EM doctors. Our study reconfirms this finding using our larger dataset, with 43 EM doctors.

TABLE 2 Demographic details by specialty

	n	Mean age at death in years (*SD*)	Causes of death (%)			%	
			#1	#2	#3	Female	Male
All specialties	8156	78.9 (14.1)	Cancer (39.1)	Heart and circulatory (26.7)	Nervous system (9.1)	15.5	84.5
Medical	1639	78.6 (14.2)	Cancer (38.7)	Heart and circulatory (26.1)	Nervous system (10.1)	11.5	88.5
Surgical	853	79.9 (13.6)	Cancer (39.4)	Heart and circulatory (27.4)	Infection (9.8)	3.4	96.6
Primary care	2508	80.3 (12.5)	Cancer (39.2)	Heart and circulatory (27.2)	Nervous system (9.6)	15.7	84.3
Anaesthesia	473	75.5 (16.1)	Cancer (41.2)	Heart and circulatory (27.6)	Infection (7.2)	18.6	81.4
Emergency medicine	43	58.7 (23.6)	Cancer (42.9)	Accidents (non-transport) (14.3)	Respiratory (14.3)	25.6	74.4
Obstetrics and gynaecology	396	78.7 (14.9)	Cancer (35.9)	Heart and circulatory (29.4)	Infection (10)	25.3	74.7
Paediatrics	397	76.1 (15.5)	Cancer (45.9)	Heart and circulatory (24.5)	Infection (7.7)	36.0	64.0
Radiology	172	75.8 (14.5)	Cancer (39.3)	Heart and circulatory (29.2)	Nervous system (11.2)	11.0	89.0
Pathology	394	79.8 (13.8)	Cancer (37.9)	Heart and circulatory (23.7)	Infection (10.6)	15.5	84.5
Psychiatry	460	76.5 (15.3)	Cancer (39.4)	Heart and circulatory (23.8)	Nervous system (8.6)	18.9	81.1
Ophthalmology	142	78.6 (14.5)	Cancer (44.2)	Heart and circulatory (26.7)	Infection (10.5)	10.6	89.4
Unknown specialty	679	80.9 (14.1)	Cancer (34.8)	Heart and circulatory (29.3)	Infection (9.1)	18.4	81.6
Emergency medicine at any time	89	71.3 (22.6)	Cancer (18)	Heart and circulatory (10.1)	Infection (6)	20.2	79.8

Note: Demographic details by specialty. Those in the emergency medicine specialty had the lowest mean age at death and a higher standard deviation. Cancer is the most common cause of death in this cohort, followed by heart and circulatory causes for all groups except emergency medicine for which it is accidental death (non-transport). The 679 people we were unable to assign a specialty to are included in the unknown specialty column and remain included in the 'all specialties' column. For comparison, a separate row is appended showing the demographic details for doctors who worked in emergency medicine at any point; this column duplicates cases held in other columns (e.g. it contains all doctors from the emergency medicine column plus 46 from the other columns). This group contains a higher than typical number of unknown causes of death.

However, these results should be interpreted with caution as EM as a specialty is only 50-year old, and so the population structure of emergency medics is different to that of other specialties. The fact that the specialty is new is the reason for the low numbers of emergency medics in the obituaries, and thus leads to censoring of older deaths, as they are yet to occur. For the other specialties with a reduced age at death, it can be reasonably assumed that the population structure is stable, given they are more established specialties. In relative survival analysis, which is compared to age matched U.K. death rates, emergency physicians are the only specialty to have a higher risk (reduced survival ratio) compared to the general population. For all other specialties 40 years after qualification relative survival compared to the general population increases dramatically, and this persists over time. The observed relative survival benefit for this cohort versus the general population does not imply causation. These outcomes are also likely to reflect socioeconomic factors on health, as this cohort is likely to be wealthier and more educated than the general population.

Specialty-specific differences in life expectancy and cause of death are also evident in longer established specialties. The average age of death amongst surgeons is significantly higher than anaesthetists and radiologists. The exact reasons for this are unknown and it is particularly interesting given that surgeons and anaesthetists share a similar work environment. Potential specialty-specific risks include exposure to volatile gases and the higher risk of substance misuse potentially due to ease of access to addictive medications in anaesthetists, for example opioids.[13–14] Prior to 1950, radiologists were at higher risk of blood and potentially solid cancers due to exposure to high levels of ionising radiation.[15] The life expectancy in radiologists is lower in our data; however, cause of death data in the radiology obituaries do not bear this out as a potential mechanism for reduced life expectancy compared to other specialties, with radiology actually having relatively lower cancer rates. Retirement age has historically differed by specialty, with primary care doctors more likely to retire earlier and less likely to return or continue part time than hospital specialists.[16] Retirement facilitates lifestyle changes associated with reduced cardiovascular disease and therefore reduced morality, for example no shift working, increased exercise and reduced stress.[17] Therefore the relatively high life expectancy in primary care may be less to do with a difference in occupational hazards but more to do with an earlier and more complete retirement.

This study has a number of limitations. It is observational and cannot demonstrate causation; however, it is well documented that practicing medicine comes with occupational hazards. Furthermore, selection bias is a limitation due to the voluntary nature of submissions

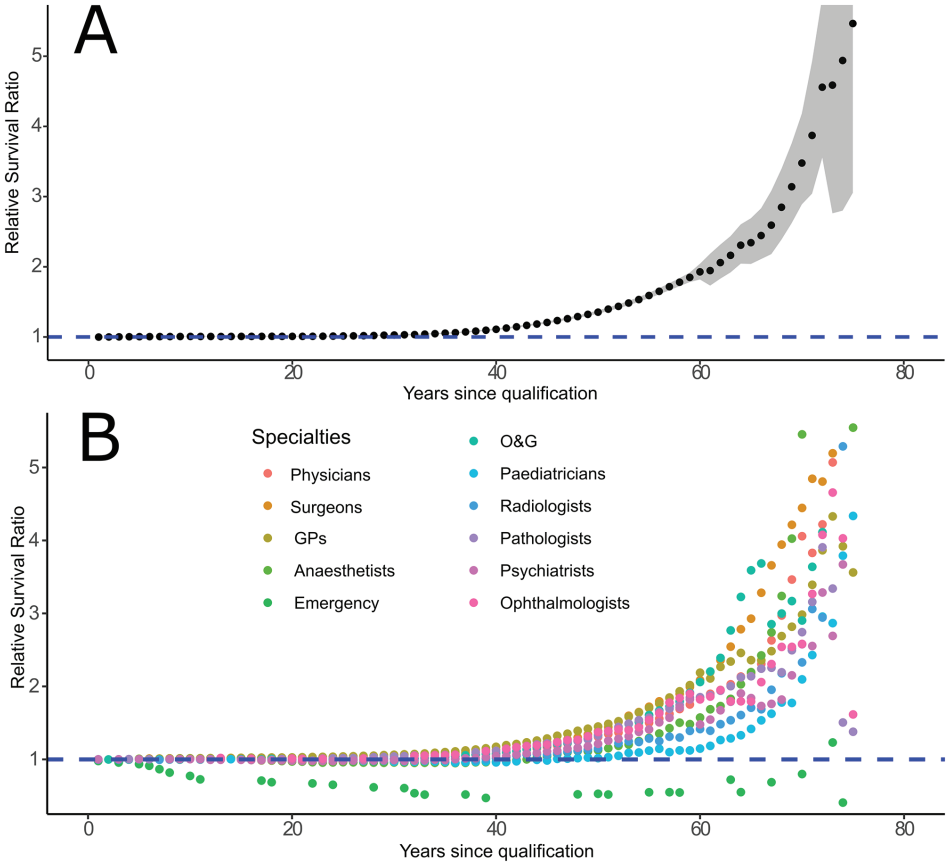

FIGURE 1 Relative survival ratio for the BMJ obituary cohort versus U.K. general population since qualification, corrected for age and year of birth (blue dashed line). (A) Relative survival ratio for all doctors with 95% confidence interval shaded in grey. (B) Relative survival ratio by specialty; note that emergency medicine has values below 1 and hence has a higher risk of death at that age

and open editorial policy, meaning that not every doctor who died in the United Kingdom has an obituary in the BMJ, and not every obituary in the BMJ is from a U.K.-based doctor. Given that the BMJ obituary data are not a formal data registry, the variables we sought to extract were inconsistently recorded. This is because the obituaries from which these data are extracted were not intended to be a repository of data, but a descriptive expression of memories, usually not written by the deceased and so prone to reporting errors. Simple demographic details were well recorded; however, specialty and cause of death were more poorly recorded. For example there is likely to be an underrepresentation of suicide in these data, as some obituaries for those who died by suicide are written in a way which suggests but does not explicitly state the cause of death. Even if fully recorded, our automated data extraction technique has an appreciable error rate in determining cause of death and specialty which should be considered when drawing conclusions.

This is the largest ever analysis of the causes of doctors' deaths in the United Kingdom. Using a novel approach of web scraping and natural language processing, we have demonstrated the value and limitations of automated data extraction. This approach gives benefits in terms of time efficiency, reproducibility and speed, but is not as accurate as manual extraction. As its application becomes more refined, and in combination with machine learning, its accuracy will improve and it may become superior to manual data extraction in every way. Even now it is opening up the possibility to analyse datasets that were previously too unwieldy to consider and may make currently time-consuming tasks such as retrospective analyses of patient notes rapid and easy.

This study follows two previous notable manual analyses of the BMJ obituary columns, in which differences in life expectancy according to birth country and specialty were described.[3,4] The data used by these studies form a subset of our data and add weight to the findings of Patel et al. regarding specialty-specific differences in age at death.[4] At a time of increasing concern regarding doctors' welfare and the impact of the career on psychological and physical health, this study demonstrates that specialty-specific differences exist. A long-term registry of medical personnel, including lifestyle data, would allow these associations to be unpicked, with construction of a regression model to explore risk factors in more detail.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from BMJ. Restrictions apply to the availability of these data, which were used with permission for this study. Data are available from the authors with the permission of the BMJ.

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AUTHOR CONTRIBUTIONS

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. ABB conceived the research concept, wrote analysis code, performed analyses and wrote the manuscript. RPB developed the research concept, wrote the scraping code, edited the manuscript and approved the final version for submission. AJF developed the research concept, wrote analysis code, edited the manuscript and approved the final version for submission. ABB affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. ABB and AJF are practising medical doctors in the United Kingdom.

ETHICAL APPROVAL

Ethical approval was not required for this study.

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ORIGINAL ARTICLE

Lifestyle interventions for healthy brain aging: A protocol for systematic review and meta-analysis

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Abstract

Background: The main objective of the present protocol is to assess the lifestyle interventions (eating habits, physical exercise, social and cultural participation) on the brain health as people age.

Methods: We will look at the following database sources, "The Cochrane Library, PubMed, EMBASE, Web of Science, and Google Scholar," for this protocol, which is standardized by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols. Only Alzheimer's disease (AD) patients will be eligible, and no restriction will be placed on participant's gender, age, education, ethnicity, or other demographic characteristics. All the studies based on the impact of active intervention centered on lifestyle interventions, including eating habits, sleep patterns, and physical exercise on the cognitive and functional status in the elderly populations. The primary outcome is the effects of nutrition and lifestyle interventions on the patients with AD, and secondary outcomes include body mass index, body fat percentage, and muscle mass.

Results: In this study, we hope to find lifestyle interventions, which could have a preventive effect on brain health as people age, in particular AD.

Conclusion: The conclusion of our study would suggest that a healthy lifestyle interventions, defined on the basis of proper nutrition, sleep patterns, physical exercise, and social and cultural activities, can positively influence the cognitive consequences of healthy brain aging.

1 | INTRODUCTION

Mental well-being is characterized by working well, feeling great, and suitably adapting the life for facing the circumstances and challenges.[1] Lifestyle choices affect mental well-being, which contributes to brain health. Previous research showed the individuals with strong community links improved mental well-being and brain health compared to the control group.[2] The social recognitions, social–economic status, family structure, and environmental factors help reduce stress.[3] The lifestyle factor that can control the cardiovascular risk factors decreases within the age-specific incidence of dementia.[4] The growing evidence suggests that diet factors with lifestyle changes improves

cognition, results in physiological aging, and prevents cognitive decline associated with dementia.[5,6] Environmental factors and lifestyle play a part in the aging; moreover, the prevalence of cognitive impairment, dementia, or neurodegenerative disorders is expected to increase with increasing aging. The prevalence of Alzheimer's disease (AD), the most prevalent form of dementia, also increases substantially with aging, as well as genetics, environmental factors, and lifestyle habits also contribute to increasing the risk. Scientists have found evidence that depression, cardiovascular diseases, vascular dementia, diabetes, and stroke could increase the risk of developing AD.[7] However, a compelling evidence suggests that brain retains its capacity for plasticity in older adults and the triad of healthy behaviors including a healthy diet along with regular physical and cognitive activity is the key for retaining this important neural property.[8] The healthy lifestyle strategies that include nutrients, food, social activities, and lifestyle that could potentially lead to better cognitive function and healthy brain aging.

This has led to the hypothesis that lifestyle interventions could have a preventive effect on neurodegenerative disorders, particularly AD.[9] Several criteria, comprising study design, dose–response relationship, heterogeneity and agreement of results over time, and identification of potential confounding factors, will be used to assess the level of evidence.[10] Therefore, in this protocol, we aim to systematically review the lifestyle interventions (proper nutrition, sleep patterns, physical exercise, socially, and intellectually active lifestyle) that may reduce the risk of brain aging.

2 | MATERIALS AND METHODS

2.1 | The registration

This protocol will follow the rules and guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015.[11]

2.2 | Inclusion criteria for study selection

2.2.1 | Study designs

We will include researches related to diet-based intervention on a reduction of caloric and fat uptake, as well as a physically, socially, and intellectually active lifestyle that may reduce the risk of cognitive decline and AD. We will consider the articles published in English only for evaluation due to language restriction and bias. Following objective assessments will be obtained from the selected studies:

1. Published documents with complete documents data;
2. Participants were confirmed to have AD;
3. Type diet based;
4. Physically, socially, and intellectually active lifestyle; and
5. The type of study design.

2.2.2 | Participants

We will include all patients suffering from AD only regardless of sex, age, racial group, education, and economic status.

2.2.3 | Interventions

Studies observing the effects of nutrition and lifestyle interventions on the cognitive functioning of patients with AD will be included. The food and nutritional interventions include dietary patterns, fruit and vegetable consumption, and a Mediterranean-type diet. The lifestyle interventions include physical exercises, social and cultural activities, and an intellectually active lifestyle. Studies comparing different types of nutritional and lifestyle intervention are also considered eligible for inclusion.

2.2.4 | Outcome

Primary outcomes are as follows: providing extensive data collection of the reported effect of assessments of diet and physical activity, sleep patterns, cognitively stimulating activities, the combination of structural brain imaging, computer-based cognitive tests, dietary pattern, family history of physically, socially, and intellectually active lifestyle that may reduce the risk of cognitive decline and AD.

Secondary outcomes could be measures of future success such as obesity indices, for example, body mass index, body fat percentage, and muscle mass.[12]

2.3 | Search strategy for the identification of studies

2.3.1 | Electronic search

The following electronic databases, "The Cochrane Library, PubMed, EMBASE, and Web of Science," will be looked at from December 2020. We will search the literature in all possible ways, including the reference lists and authors' files from the included studies, in the protocol.

2.3.2 | The search terms for PubMed

In order to collect the literature comprehensively, a wide range of terms (and related truncations, e.g., "cognit*" to tap cognitive and cognition) will be used. These were "Alzheimer's disease" or "AD" or "Alzheimer-type dementia" or "cognitive decline" or "physical activity" or "cognitive function" or "diabetes" or "neurocognitive" or "structural brain imaging" or "computer-based cognitive tests" or "nutrient" or "food" or "dietary pattern" or "western diet" or "health behavior change" or "Brain-Body Connection" or "Brain Food connection" or

TABLE 1 Search strategy for the PubMed database

Number	Search item
1	Alzheimer's disease
2	Alzheimer-type dementia
3	Cognitive decline
4	Physical activity
5	Cognitive function
6	Diabetes*
7	1 or 2–6
8	Cognit*
9	Cognitive neuroscience
10	Cognition disorders
11	Neurocognitive
12	Neuropsychological tests
13	9 or 10–12
14	Neuroimaging
15	Structural brain imaging
16	Computer-based cognitive tests
17	Functional neuroimaging
18	14 or 15–17
19	Nutrient
20	Food
21	Diet
22	Dietary pattern
23	Western diet
24	19 or 20–23
25	Brain-Body connection
26	Brain Food connection
27	Brain ageing
28	Cognition and diet
29	25 or 26–28
30	Randomized control trial
31	Randomized
32	Health behavior change
33	30 or 31–32
34	7 and 13 and 18 and 24 and 29 and 33

Brain Ageing, Cognition and Diet (Table 1). Combinations of Medical Subject Headings (MeSH) and text words will be used. The same search term will be used in other electronic databases.

2.4 | Data collection and analysis

2.4.1 | Selection of studies

We chose the PRISMA flowchart to show the process of selecting literature for the entire study (Figure 1). Before searching the literature, all reviewers will discuss and determine the screening criteria. After defining the screening requirements clearly, the two reviewers will separately review and screen the titles and abstracts extracted by the search against the inclusion criteria excluding duplicates or studies with missing information. Afterward, the two reviewers will scan full-text reports and decide whether or not those studies meet the inclusion criteria in order to get the qualified studies. The obtained literature will be managed through EndNote software V.X8 (Thomson Corporation, United States). Any inconsistencies will be resolved through discussion with a third investigator.

2.4.2 | Data extraction and management

The reviewers will assess the studies' eligibility independently using the inclusion and exclusion criteria. The following data will be extracted from the included studies using a data collection form and recorded in an excel sheet: first author and year of publication, study design, participants, clinical features, Diagnostic criteria, assessment type, cognitive assessment type, type of food, and funding sources. All data will be transferred into Review Manager Software (RevMan V.5.3) for analysis and synthesis.

2.4.3 | Assessment of risk of bias in included studies

Two authors will separately assess the methodological quality of every study according to the standards advised by the Cochrane Handbook for Systematic Reviews of Interventions. Any disagreements will be discussed with a third reviewer for reached consensus and resolution.

2.4.4 | Measures of treatment effect

In this protocol, we will use a 95% confidence interval (CI) risk ratio to meticulously analyze the dichotomous data. As for the continuous data, weight means difference or standardized mean difference will be used to measure the efficacy of 95% CI. Skewed and nonquantitative data will present descriptively.

2.4.5 | Unit of analysis issues

Preliminary analysis will be performed on the participants who are assigned by random sampling methods. The issue and concern are always present for the studies of cluster randomized trials or studies with multiple treatment groups and no proper standard design in literature research. We will follow the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions for clustered randomized trials and multiple treatment groups. We will show the additional treatment arms for multiple treatment group's studies. The studies will not be considered where the additional treatment arms are not relevant in study design.

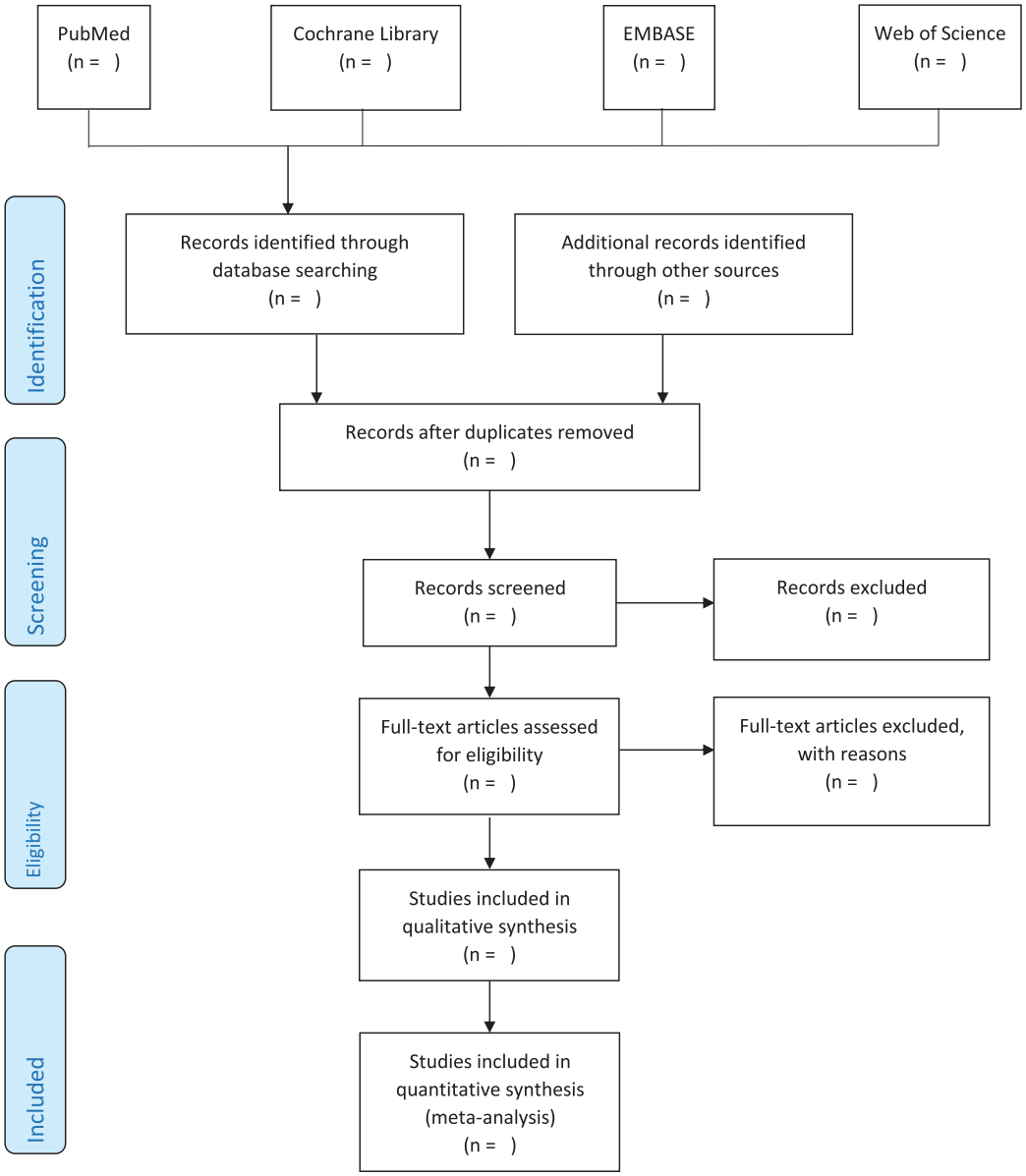

FIGURE 1 Flow chart of the study. Adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)

2.4.6 | Management of missing data

We will do everything in our best to ensure the integrity of our data. If there are missing data, we will try our best to contact the corresponding author of the article through emails, phone calls, and so forth. If the corresponding author cannot be reached, we will use sensitivity analysis to assess the impact of the missing data on the outcome; if the impact is significant, we will then remove the experiment with the incomplete data. After ensuring the integrity of the data, intention analysis therapy and sensitivity analysis will be performed.

2.4.7 | Assessment of heterogeneity

For detecting statistical heterogeneity, the Chi^2 test (significance level: 0.1) and I^2 statistic will be used to test the heterogeneity among trials. The values of I^2 are divided into the following: <40% means "might not be important"; $30\% < I^2 < 60\%$ means "represent moderate heterogeneity"; $50\% < I^2 < 90\%$ means "substantial heterogeneity"; $75\% < I^2 < 100\%$ means "considerable heterogeneity." If high levels of heterogeneity are noted among the trials ($I^2 \geq 50\%$ or $P < .1$), the study design and characteristics in the included studies will be analyzed, and subgroup analysis or sensitivity analysis will be used to explain the heterogeneity.

2.4.8 | Data synthesis

Each outcome will be calculated and combined with the use of RevMan 5.3. The Specific application was based on the current version of the Cochrane Handbook for Systematic Reviews of Interventions. If the tests of heterogeneity are not significant, the Mantel–Haenszel

method will be chosen for the fixed-effect model, and if the statistical heterogeneity is observed ($I^2 \geq 50\%$ or $P < .1$), then the random-effects model will be used. If heterogeneity is significant, we will perform a narrative, qualitative summary.

2.4.9 | Assessment of reporting biases

In this analysis, once we include over 10 trials, funnel plots may be used to test for reporting bias.

2.4.10 | Subgroup analysis

Given that individual studies may consist of multiple treatment groups, subgroup analysis will be done to explain heterogeneity if possible. The following factors, among others, will be considered:

1. Patient's characteristics (age, sex, underlying diseases);
2. Neuroimaging studies;
3. Diabetes;
4. Hyperlipidemia;
5. Hypertension;
6. Prediabetes; and
7. Metabolic syndrome.

2.4.11 | Sensitivity analysis

We will perform the sensitivity analysis according to sample size, study design, heterogeneous quality, methodological quality, and statistical model. Any trials with defects in quality will be excluded guaranteeing the stability of the analysis results.

2.5 | Ethical review and informed consent of patients

The content of this article does not involve moral approval or ethical review and will be presented in print or at relevant conferences.

2.6 | Data sharing statement

The data that support the findings of this study will be available as the Supporting Information of this article.

3 | DISCUSSION

This protocol will highlight the importance of the use of certain nutrients, foods, and dietary patterns that could improve cognitive outcomes.[13] This protocol will support the brain health initiative for eating habits and lifestyle intervention, which could improve the health and cognitive decline across the AD.

This protocol will provide the evidence that eating habits (vitamins, minerals, virgin olive, vegetables, fruits, plant proteins, whole grains, and fish) could decrease the risk of AD and improve cognitive functions, as well as healthy brain aging. For supporting the evidence of our protocol, Scarmeas et al. showed that high adherence to Mediterranean food reducesed the risk for AD.[14] The subjects with moderate adherence to Mediterranean food could reduce the risk of developing AD by 15%–21%, whereas those with high adherence had 39%–40% fewer chances of developing AD.14 Thus, cognitive decline in AD can be improved by strongly adhering to Mediterranean food over 1.5 years.[14] In another study, Berti and colleagues observed that higher Mediterranean diet adherence provides a 1.5–3.5 years' delay in the progression of AD and protection against brain aging and AD.[15] A comprehensive understanding of the link between brain health and eating habits with lifestyle programs is lacking, which could be improved through the meta-analysis for brain health to benefit society, especially the aged population and patients with AD. Moreover, our protocol will expedite some methods and gaps to study the prevention and treatment effect of lifestyle interventions for healthy brain aging in the future.

AUTHOR CONTRIBUTIONS

Shahid Bashir, Eman Nasim, Mohammad Uzair, Asim Niaz, and Syed Shahid Habib conceptualized the study. Shahid Bashir, Aneesa Zafar, Ghulam Murtaza, Kaleem Imdad Ali, and Muhammad Arshad done the literature research. Shahid Bashir, Mohammad Uzair, and Fawaz Al-Hussain reviewed and edited the manuscript. All authors reviewed and approved the final draft.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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