Seeking a pot of gold with integrated behavior therapy and research to improve health equity: insights from the RAINBOW trial for obesity and depression

Elizabeth M. Venditti,[1] Lesley E. Steinman,[2] Megan A. Lewis,[3] Bryan J. Weiner,[4] Jun Ma[5]

[1]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

[2]Health Promotion Research Center, University of Washington, Seattle, WA, USA

[3]Research Triangle International, Seattle, WA, USA

[4]Departments of Global Health and Health Services, University of Washington, Seattle, WA, USA

[5]Department of Medicine and Institute of Health Research and Policy, University of Illinois at Chicago, Chicago, IL, USA

Correspondence to: Elizabeth M. Venditti, vendittiem@upmc.edu

Abstract

More than one third of adults in the United States (U.S.) live with multiple chronic conditions that affect their physical and mental health, functional outcomes, independence, and mortality. The COVID-19 pandemic has exposed not only an increased risk for infection, morbidity, and mortality among those with chronic conditions but long-standing health inequities by age, race, sex, and other social determinants. Obesity plus depression represent one such prevalent comorbidity for which few effective integrated interventions exist, prompting concern about the potential for secondary physical and mental health pandemics post COVID-19. Translational behavioral medicine research can play an important role in studying integrated collaborative healthcare approaches and advancing scientific understanding on how to engage and more effectively treat diverse populations with physical and mental health comorbidities. The RAINBOW (Research Aimed at Improving Both Mood and Weight) clinical trial experience offers a wealth of insights into the potential of collaborative care interventions to advance behavior therapy research and practice. Primary care patients with co-occurring obesity and depression were assigned to either Integrated Coaching for Mood and Weight (I-CARE), which blended Group Lifestyle Balance (GLB) for weight management and the Program to Encourage Active Rewarding Lives (PEARLS) for depression, or usual care, to examine clinical, cost-effectiveness, and implementation outcomes. This commentary highlights the empirical findings of eight RAINBOW research papers and discusses implications for future studies, including their relevance in the U.S. COVID-19 context. Organized by key principles of translational behavioral medicine research, the commentary aims to examine and embrace the heterogeneity of baseline and intervention response differences among those living with multiple chronic conditions. We conclude that to prevent health and healthcare disparities from widening further, tailored engagement, dissemination, and implementation strategies and flexible delivery formats are essential to improve treatment access and outcomes among underrepresented populations.

INTRODUCTION

People living with two or more chronic conditions (i.e., multimorbidity) have more self-care difficulties, utilize more services, and experience significant

Implications

Practice: When obesity and depression occur together they may be treated effectively using an integrated collaborative care team approach, focused on person-centered goals.

Policy: Tailored engagement strategies, rapid dissemination and implementation of evidence-based practices, and access to digital support technologies are urgently needed to advance health equity for persons living with chronic physical and mental health conditions, especially in under-resourced communities.

Research: Translational behavioral medicine studies should continue to examine optimal, cost-effective ways to disseminate and implement integrated mind-body healthcare to people at highest risk for chronic disease.

health, physical and social functioning, and financial burdens [1]. Multimorbidity is prevalent in adults of all ages and affects the vast majority of those age 65 and older [1]. Systemic racism, known to be associated with unfavorable psychological, social and environmental impacts (e.g., experiences of racial discrimination, trauma and loss, poverty) likely influences multiple disease pathways [2] leading to conditions such as obesity, hypertension and diabetes. Research clearly supports that Black, Indigenous, and People of Color (BIPOC) have borne a disproportionate share of the burden of these multimorbid conditions compared with non-Latino White people [3–7]. Emerging epidemiologic research also indicates that multimorbidity including elevated depressive symptoms is also linked to worse health outcomes [8, 9].

In the COVID context, multimorbidity presents unique susceptibility to infection, complications, and death [10, 11]. A report from the U.S. Centers for Disease Control and Prevention found that persons with underlying chronic conditions were six times as likely to be hospitalized and 12 times more likely to die from COVID-19, with BIPOC communities

bearing disproportionate burden [12]. A systematic review in Annals of Internal Medicine has indicated, with moderate-to-high confidence, that African American/Black and Hispanic populations have 3.2 times the risk for mortality compared with White populations, although they experience similar case fatality rates, suggesting that unequal health care access and exposures pose the greatest threat [13]. Black or African American people have lower absolute rates of depressive disorders compared to White people, but they have higher rates of functionally impairing symptoms, and less access to quality mental health care [14]. The medical anthropologist, Charles C. Gravlee [4] and others have argued that an explicit conceptual framework is needed to address the synergistic forces (e.g., "syndemic" theory) [15] that shape cardiometabolic population health in normal times, let alone during a pandemic. In this light, the co-occurrence of obesity and depression represent important target risk factors for morbidity and mortality, and for which effective, integrated, and accessible treatments are clearly needed.

An integrated approach to assessment and treatment of physical and mental health conditions has long been recognized for its potential to provide better, more efficient, person-centered, preventive and coordinated care compared with usual care [16, 17]. Further, there is a pressing need for studies to examine optimal ways to deliver integrated healthcare to people in communities with disproportionately high levels of mental and physical health burden. Indeed, most conceptual frameworks and research on the social determinants of mental health regard physical health and mental health as inextricably intertwined [18]. Thus, rapidly disseminating and implementing evidence-based practices in relevant settings, and using digital support technologies for remote delivery is crucial, in the COVID-19 context and beyond [19]. In this commentary, we highlight findings from eight empirical papers from a recent randomized clinical trial of an integrated depression and obesity intervention (I-CARE) using guiding principles of translational behavioral medicine research [20−23]: (a) patient-centered outcomes (treat the person); (b) health equity (treat all persons); (c) tailored and personalized interventions; (d) optimized interventions; (e) affordable, cost-effective interventions; and (f) broad public health impact interventions.

Development of I-CARE

Grounded in social cognitive theory [24], I-CARE blends elements of the Group Lifestyle Balance (GLB) intervention [25] derived from the Diabetes Prevention Program designed to address weight and cardiometabolic risk [26, 27], and the Program to Encourage Active, Rewarding Lives (PEARLS) for depression care management using a collaborative stepped-care model [28, 29]. Both interventions

were validated independently in efficacy trials [20, 29−31]. Leveraging synergistic elements (e.g., goal setting, weekly self-monitoring, problem-solving, behavioral activation), I-CARE provided six months of active treatment followed by six months of maintenance care, as described extensively in our protocol design paper [32] and depicted in Fig. 1). I-CARE mood sessions were a primary focus during the initial six weeks of intervention, employing structured problem-solving and behavioral activation strategies as a first-line therapy supplemented with stepwise increases in dose and number of antidepressant medications as needed. Lifestyle sessions and progress checks were incorporated thereafter to promote modest (5%−10%) weight loss through healthy dietary change, moderate calorie restriction, and physical activity of ≥150 min per week. The I-CARE team, which included a health coach, intervention manager, psychiatrist, and primary care physician, held group meetings weekly for case review. The psychiatrist did not meet with the participant directly but made recommendations to initiate or adjust antidepressants followed a structured protocol managed by the patient's regular care provider.

Principle 1: Patient centered outcomes − treat the person

The RAINBOW trial [33] was the first examination of whether I-CARE would significantly improve weight loss [body mass index (BMI kg/m^2) change] and depressive symptoms (SCL-20) at 12 months, compared with usual care, among 409 primary care patients with comorbid obesity and depression. Participants were 70% non-Latino White, mostly female and college-educated, and mean age of 51 years. The co-primary outcomes, reported at 12 months, were that BMI and depression declined significantly among intervention participants compared with controls (between-group mean difference: BMI, −0.7 [95% CI, −1.1 to −0.2]; SCL-20 scores, −0.2 [−0.4 to 0]). Secondary categorical outcomes showed that significantly more intervention than usual care participants achieved ≥5% weight loss and ≥50% reduction or full remission in depression symptoms at 6 months. Between-group differences in these categorical outcomes were maintained at 12 months for weight loss only. Secondary analyses [34] demonstrated that I-CARE conferred significant improvements in obesity-specific problems (e.g., being bothered by weight when trying on clothes), mental health-related quality of life, sleep problems, and functional disability at six months, but not at 12 months, when compared with usual care.

These findings are consistent with other studies that underscore the importance of developing feasible continued-contact strategies for adults with multimorbidity to better maintain treatment effects (e.g., incorporating remote delivery for scalability) [19, 35]. The modest I-CARE effect sizes also provide impetus to examine heterogeneity in treatment
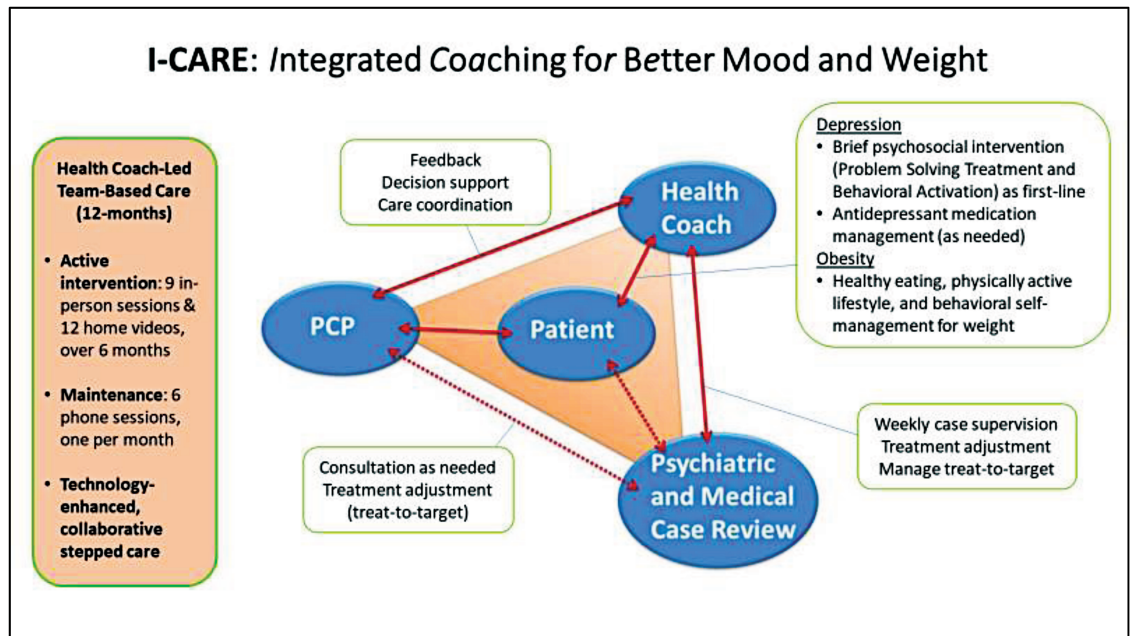
Fig 1 | I-CARE intervention developed for the RAINBOW trial

response and baseline characteristics, understand effect moderators and mediators, and explore predictors of early engagement and adherence. This research expansion can strengthen specific intervention components and apply them with greater precision, thereby better tailoring and targeting I-CARE for individuals or different subpopulations to promote equity and improve outcomes [36].

Principle 2: health equity – treat all persons

The National Institutes of Health expects sex and gender to be considered in all research designs. A full accounting on this topic is beyond the scope of this commentary, but it is understood that self-reported biological sex as was ascertained in RAINBOW (i.e., male or female, in this report used synonymously with men or women) has psychosocial and socioeconomic implications for treatment engagement and health outcomes beyond genetics. Prior studies support probing sex-specific responses to treatment to inform therapy development and address health equity [37, 38]. The lifetime prevalence of obesity is similar for men and women in the United States (roughly 40%) [39]; however, for diagnosed major depressive disorder, lifetime prevalence is significantly higher in women (26%) compared with men (15%) [36] as is subclinical depression [40]. Further, in contrast to men with obesity, women with obesity appear to have higher rates of concurrent depressive disorders [41].

Indeed, RAINBOW [20] showed that sex was a significant effect modifier of I-CARE at 12 months: men demonstrated greater improvement than women in BMI, whereas women demonstrated significantly greater reductions than men in depressive symptoms. Post hoc analyses showed that sex

significantly modified I-CARE effects on weight loss and depression outcomes over 24 months [42]. Men achieved significantly greater reductions than women in BMI and percent weight loss at each follow-up time point (6, 12, and 24 months) in the intervention relative to usual care. Conversely, compared with men, women improved their SCL-20 (depression) scores more with I-CARE relative to usual care at 12 and 24 months.

These findings confirm biological sex as an important a priori moderator to consider for research on integrated collaborative care interventions for obesity and depression. As opposed to one-size-fits-all treatment protocols, targeting specific components and strategies to help women and men may be warranted. It may also be advantageous to study sex-specific cut-points for the observed risks and benefits, or as indicators of treatment progress. While RAINBOW demonstrated I-CARE's differential impact by sex, the study sample lacked sufficient diversity to look at heterogeneity in health outcomes by race, ethnicity, or age. The recently completed ENGAGE-2 trial [43], intended to evaluate the generalizability of I-CARE, will provide quantitative and qualitative data on a sample comprised of 58% Black and 26% Hispanic or multiracial individuals, further addressing questions of treatment engagement and effectiveness among underrepresented communities with fewer healthcare resources.

Principle 3: Tailored and personalized interventions

A comprehensive understanding of baseline differences among individuals receiving evidence-based interventions is inherent to translational behavioral medicine, which strives to improve targeting and engagement strategies to enhance effectiveness

according to a precision health framework [44]. Patients with the same diagnosis rarely present with uniform constellations or severity of signs and symptoms, but few studies have focused on profiling patients with co-existing obesity and depression to explore phenotypic differences. Ma et al. [45] analyzed the baseline profiles of RAINBOW participants categorized into four comorbidity severity groups according to binary levels of BMI and depression symptom scores using clinically relevant cut points: BMI of ≥35.0 for high severity obesity and an SCL-20 score of ≥1.5 for high severity depression. Baseline profiles, by comorbidity severity category, were based on sociodemographic characteristics (e.g., age, sex, race, income), behavioral indices (e.g., diet, problem-solving orientation), clinical features (e.g., blood pressure, anxiety), and psychosocial functioning (e.g., mobility, self-care, pain).

RAINBOW participants with a high severity "obesity dominant" phenotype, regardless of depression severity, had unfavorable scores on most cardiometabolic measures and low levels of physical activity. Regardless of obesity severity, those with a high severity "depression dominant" phenotype had negative and avoidant problem-solving styles, greater affective symptoms, poorer health-related quality of life, more obesity-specific psychosocial problems, greater sleep problems and disability. By examining a constellation of important somatic and affective baseline characteristics, then accounting for their severity, this study added to our understanding of a complex comorbid population and may inform future targeting and engagement studies.

In addition, understanding individual variability in early engagement, self-monitoring behaviors, and subsequent weight or depressive symptoms over the course of treatment (not simply pre-post endpoints) can advance personalized care. Data on weight self-monitoring and PHQ-9 scores obtained over the 12-month intervention period [46] indicated that 31% of I-CARE patients had poor engagement. This group tracked their weight, on average, less than three weeks out of 12-months and attended fewer than five sessions out of 15. Among those engaged, three patterns of progress were observed for weight loss (minimal, moderate, substantial) and for depression (moderate depression without treatment progress, moderate depression with treatment progress, and mild depression with treatment progress). Poor engagement and response patterns were identified within six to eight weeks of intervention onset, suggesting potential triage points at which augmentation or ancillary treatments should be considered. By monitoring trajectories, future research can offer new insights and guidance for the development of integrated interventions.

Principle 4: Optimized interventions

The article by Rosas and colleagues published in this journal [47] examined putative behavioral and lifestyle mechanisms by which I-CARE may have improved weight and mood. Compared with usual care, I-CARE resulted in decreased calorie intake and increased physical activity at 6 but not 12 months. Regardless of randomization group, increased fruit and vegetable intake and a decreased avoidant problem-solving style were associated with improved depressive symptoms and BMI at 6 and 12 months. Higher dietary quality, overall problem-solving ability, changes in negative problem orientation and an impulsivity/carelessness problem-solving style were also significantly correlated with depression improvement at 6 and 12 months in both groups. However, the hypothesized mediation pathways linking these variables to weight and depression outcomes as a result of I-CARE were not significant, perhaps explaining why effect sizes were not more robust.

These results were nonetheless informative, especially in context of well-known findings[20, 28, 29, 48] regarding the centrality of problem-solving skills in depression treatment, and the need to target maintenance behaviors for relapse prevention in weight self-management after an intensive induction period. Improving nutrition quality has long been a feature of behavioral weight management, but less frequently used in depression interventions [49, 50] and warrants further study. Evaluation of hypothesized mediators for increasing behavioral activation in the early stages of intervention for comorbid obesity and depression represents another important research area for mind-body health. Tailoring strategies to improve lifestyle behaviors and cognitive style should be targets of future intervention trials to maximize I-CARE's short- and long-term effectiveness. Furthermore, multi-level research studies which align individual-level behavioral and problem-solving interventions with public health policy approaches to increase access to healthful foods and physical activity may also be necessary to optimize health interventions for persons experiencing food insecurity, or unsafe neighborhoods, or sheltering-at-home due to COVID-19 and other environmental concerns.

Principle 5: Affordable and cost-effective interventions

Goldhaber-Fiebert et al. expanded understanding of I-CARE's effectiveness by examining outcomes from both a healthcare system and patient perspective: cost of care and health-related quality of life [51]. This study calculated the 1-year implementation cost of I-CARE at $2,251 per person based on staff time for the lifestyle coach, intervention manager, and consulting physician and psychiatrist. I-CARE significantly increased the number of antidepressant medications prescribed compared with usual care participants over time, without significant change in annual spending on healthcare services. In other words, collaborative medication management

for patients with co-existing obesity and depression has potential to provide better care at better value than usual siloed care.

The ultimate economic value of the I-CARE approach depends on whether shorter-term improvements in both obesity and depression result in longer-term improvements in morbidity and mortality and lower costs of care. Employing the threshold for an intervention to cost less than $50,000 per Quality Adjusted Life Year (QALY), this study modeled projections for I-CARE's cost of care findings by 20 years. Results showed that 0.045 QALYS would be needed for I-CARE to be cost-effective as compared to the observed 0.011 QALY improvement after one-year of I-CARE. The authors [51] concluded that I-CARE could be cost-effective if first-year improvements were associated with maintained lower levels of depression and improved morbidity and mortality resulting from reduced obesity. Even small ongoing health benefits, short of complete remission, have value if they translate to decreases in future medical utilization and costs because of better controlled multimorbidity, highlighting the importance of doing cost-effectiveness studies of different case-management and implementation strategies. In summary, more potent treatment effects early on and good maintenance care have potential to reduce the burden of complex comorbidities for both providers and patients.

Principle 6: Broad public health impact interventions

Lewis and colleagues [52] evaluated I-CARE's potential for public health impact using RE-AIM [53] (reach, effectiveness, adoption, implementation, and maintenance) a well-established implementation science evaluation framework. This evaluation examined the experiences of participants and the providers and program staff involved in intervention delivery. Conclusions were that to enhance program *reach*, offering greater scheduling flexibility could increase program accessibility. Many I-CARE participants reported that a one-year time commitment increased their willingness to participate since it suggested the program was worthwhile. However, time commitment represented a barrier to others given competing work or commute schedules or concerns about staying motivated over one year. Participants shared that having a flexible job schedule, more motivation for change, a health coach, and a convenient location to do the intervention facilitated participation. I-CARE providers believed that sensitivity to potential stigma about depression and obesity, taking the necessary time, energy, and resources to review medical charts to identify appropriate patients for treatment were important for increasing program participation. They also recommended outreach to other providers (e.g., registered dieticians) and integrating recruitment into electronic health records to bolster program engagement.

To increase program *effectiveness,* this evaluation suggested that tailoring I-CARE components to patients' dietary, physical activity, or problem-solving needs rather than delivering a standard curriculum could enhance engagement and retention. Participants who employed I-CARE skills (e.g., problem-solving and goal setting, diet and exercise monitoring, and integration of physical activity into their daily routine) expressed program satisfaction and an ability to address barriers such as stress, competing demands, limited time and motivation when managing their weight and mood. Some participants desired greater program flexibility and accountability beyond individual I-CARE coaching sessions. Further research is needed to understand and address patient needs and expectations for person-centered yet structured behavioral interventions—e.g., setting realistic goals for persons with severe depression and/or multiple intersecting social determinants of health, and building in social and community support to aid progress inside and outside of treatment settings.

The evaluation also indicated that providers and other health system leaders identified "buy-in" across clinical service lines as a key factor in potential program *adoption.* Because I-CARE is a collaborative care approach, dietitians, psychiatrists, and primary care physicians, and their managers, needed to coordinate treatment to ensure fidelity when adopting the program. Clinicians and intervention staff also noted potential advantages of the integrated collaborative care approach for alleviating time pressures experienced when treating patients with comorbid obesity and depression independently. Coordination and communication among interdisciplinary team members delivering I-CARE further highlighted important *implementation* considerations. As the team members developed trust and rapport, and increased commitment to the program, they observed efficiencies in delivering coordinated care (including medication management) across multiple clinics in the care system.

Lastly, I-CARE benefits were more likely to be *maintained* when participants reported intent and confidence to continue using goal-setting and problem-solving strategies. However, systemic changes such as improving access to mental healthcare, adequate staff, and resources, and integrating I-CARE behavior change strategies for weight and mood management into primary care treatment standards was also seen as needed for increasing implementation and effectiveness. These findings have workforce training, practice standards, and healthcare infrastructure implications if organizations are to be able to sustain evidence-based interventions such as I-CARE.

Summary of research insights

I-CARE empirical findings have enabled multiple insights into behavior therapy research and practice

to improve the health and well-being of persons living with multiple chronic conditions—specifically, the comorbidity of obesity and depression. First, I-CARE was effective in helping high-risk participants improve not only clinical outcomes of weight and mood [33], albeit modestly, but also important patient-centered outcomes (Principle 1) such as health-related quality of life, sleep problems, and functional disability [34], thus reducing patient and provider health burdens. To treat the whole person, I-CARE leveraged goal setting, self-monitoring, behavioral activation, and problem-solving for self-management of physical and mental health and provided linkages to clinical supports and services as needed. This aligns with Glasgow's definition of intervention "effectiveness" in RE-AIM (23) and underscores the need to include broader patient-centered outcomes such as quality of life to insure that health disparities and burdens are being addressed.

Second, I-CARE studies suggest researchers should anticipate and embrace, not ignore, the heterogeneous baseline profiles and intervention effects of evidence-based therapies and plan to tailor implementation accordingly (Principles 2 and 3). From health marketing and outreach, to initial engagement and adherence monitoring, to longer-term maintenance, heterogeneity of subgroups appears to be the rule rather than the exception. Future research should focus on adaptations to both the I-CARE intervention and specific implementation strategies to improve BMI response among women, and depressive symptoms among men. One opportunity is to enhance the active intervention phase to address secondary outcomes like sleep [34] that are associated with improvements in both BMI and SCL-20, or to target cognitive and lifestyle functions like avoidant problem-solving style, problem-solving abilities, fruit and vegetable intake, and overall dietary quality to optimize the effects of I-CARE [47].

Likewise tailoring I-CARE to different depression and obesity severity profiles and assessing, a priori, which condition is more dominant may further optimize the base intervention to improve health for different subpopulations (Principle 4). For example, the intermediate severity profile had lower abdominal obesity, higher physical activity, and greater obesity-specific and mental health-related quality of life problems (higher anxiety, depression, pain and discomfort), thus may need greater focus on problem-solving, behavioral activation and medication over the course of all I-CARE [45]. Multiphase Optimization Strategy Trials (MOST) and Sequential Multiple Assignment Randomized Trials (SMART) [54] would facilitate optimization of testing I-CARE intervention components and tailoring of interventions for patient subgroups, instead of delivering the same intervention to all participants. Our recently completed ENGAGE-2 study is evaluating I-CARE within a highly diverse population (comprised of Black, Latino, and persons of lower socioeconomic status) to examine benefits for persons with greater inequities in access to quality care and health-related outcomes [43]. This study will provide further insights in how to tailor both interventions and their implementation to promote rather than exacerbate health inequities.

Third, differences in I-CARE engagement and adherence suggest tailoring opportunities for targeted I-CARE outreach, dissemination, and implementation well before participant dropout or ineffectiveness is manifest. Further, the RE-AIM evaluation identified facilitators to strengthen and barriers to overcome which could maximize program reach, effectiveness, adoption, implementation, and maintenance. Future research and practice should integrate I-CARE into standard practice, look at return on investment to incentivize health systems and reimbursement, and tailor the intervention to be more personal and address specific patient barriers (Principles 5 and 6). Given the disproportionate burden of multiple chronic conditions faced by BIPOC communities, and now increased mortality risk and decreased access to care presented by COVID-19, further I-CARE research must explicitly prioritize these minoritized communities. Shelton and colleagues' recent adaptation of RE-AIM to promote equity [55] provides one model for improving I-CARE's effectiveness and reach among minoritized and under-resourced populations.

Fourth, the COVID-19 pandemic has illuminated the disproportionate health and healthcare burdens faced by BIPOC communities after centuries of systemic racism. In addition to targeting and tailoring I-CARE towards populations that have not been effectively served by mainstream healthcare systems, future translation research must address specific barriers to accessing different modes of care (face-to-face or digital) and determine whether multi-level interventions including additional therapies, care-management navigation, or health policy decisions are required to implement I-CARE [56]. Future research and practice should engage and train community health workers and other community-based providers who have the trust and rapport of disadvantaged populations [57, 58]. Well trained and supported community care providers such as health coaches or lifestyle coaches, working in concert with other professionals (e.g., registered dieticians, psychiatric specialists, primary care providers), can address workforce shortage issues. They can expand reach to under-resourced communities burdened by multiple chronic conditions that simply do not have critical healthcare services [59]. Hybrid dissemination and implementation trials [60, 61] study how to best improve intervention reach and delivery in new contexts while continuing to evaluate program

effectiveness, and would be an appropriate next step in I-CARE's evaluation.

CONCLUSIONS

Harnessing insights from the RAINBOW trial as an example of an integrated collaborative care intervention to treat multiple chronic conditions, specifically obesity and depression, we propose that accelerating the research focus on targeted and tailored engagement, dissemination, and implementation strategies to improve intervention access, response, and outcomes among under-resourced groups is especially urgent to prevent health disparities from widening further following the COVID pandemic. This fits the vision for practice-based translational behavior change research, where clinical and public health practice-embedded research is conducted on the implementation, optimization, and fundamental mechanisms of behavioral interventions [62].

Glossary:

RAINBOW: Research Aimed at Improving Both Mood and Weight

I-CARE: Integrated Coaching for Mood and Weight

GLB: Group Lifestyle Balance

PEARLS: Program to Encourage Active Rewarding Lives

BIPOC: Black, Indigenous, and People of Color

BMI: Body Mass Index kg/m^2

SCL-20: 20-item Depression Symptom Checklist

Compliance with Ethical Standards

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Human Rights: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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