WOMEN IN SCIENCE: PUBLIC HEALTH EDUCATION AND PROMOTION 2021

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WOMEN IN SCIENCE: PUBLIC HEALTH EDUCATION AND PROMOTION 2021

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Editorial: Women in science: Public health education and promotion 2021

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Editorial on the Research Topic
Women in science: Public health education and promotion 2021

Although progress in the representation of women in science, technology, engineering, mathematics, and medicine (STEMM) is slow to improve, the number of women holding STEMM faculty positions has remained stagnant or declined (1, 2). In Italy and Norway, for example, females are underrepresented in top research positions despite performing as well as their male counterparts (3). Gender inequality in scientific careers has been demonstrated by differences in productivity, citation, and salary metrics (4). Further, a disparity exists with fewer women authors from wealthy countries (i.e., Germany, Switzerland, Japan) compared to poorer countries (i.e., Serbia, Romania, Bosnia Herzegovina) (2). Potential contributing factors for these discrepancies could include prevalent gender stereotypes, absence of social capital in the form of support networks, unwelcome academic and research environments, cultural factors, and the overlap of establishing a research career with motherhood, childcare, and family obligations (1, 2). Despite improvements in the promotion of women in science, such as the National Science Foundation's ADVANCE initiative which promotes equity for faculty in the academic profession, systemic and organizational reforms in the promotion trajectory, including education, publishing, and mentoring are needed as a start to close the gender gap in academia (2, 5).

To serve as a mechanism by which to highlight the contributions of women researchers, this Research Topic features female contributions to Public Health, specifically in the field of Public Health Education and Promotion. The theme, intentionally broad in scope, sought general perspectives on a specific field of research inspired and initiated by women; articles celebrating outstanding female researchers and their contributions to public health education; and research studies led by women

studying public health education and/or health promotion. To be considered for this collection of articles, the first or last author was required to identify as female. Lastly, it was recommended that early career researchers collaborate with senior female colleagues. This editorial aims to provide an overview of the key findings of the papers published in the Research Topic on Women in Science—Public Health Education and Promotion, 2021. Upon review of the articles, most research addressed maternal health issues but extended into disparate, yet contributory areas including the COVID-19 pandemic, cholera, upper respiratory infections, physical activity, and the experience of Latina women in academia. The types of articles received in response to this Research Topic were comprehensive including original research, perspectives, brief research report, study protocol, systematic review, and a community case study. The authors' work is organized and summarized according to article type below:

Original research

Upper respiratory tract infections (URTIs) are primarily viral with many of the reported cases being bacterial. Defining and differentiating such patients is difficult because the clinical presentations connected with bacterial or viral-related URTIs commonly overlap, hence antibiotics are frequently prescribed to manage URTIs in primary care settings. Nevertheless, and other than certain exceptions, antibiotics are unnecessarily prescribed for URTIs. This frequent use of antibiotics adds a burden to healthcare systems that results in clinical failure and/or an increase in the development of antibiotic resistance. Hashmi et al. conducted a retrospective prescription analysis to document URTI-specific antibiotic prescription frequency in a public primary healthcare setting of Quetta City, Pakistan. Prescribing practices were evaluated based on the recommendations of the National Institute for Health and Care Excellence. The authors found that antibiotics were frequently prescribed for non-specific URTIs, cough, and rhinitis, even though only a limited number of patients with URTIs warranted antibiotic treatment. The authors propose developing and implementing local antibiotic guidelines and continuous medical education regarding antibiotic use. The authors also urge policymakers to introduce antimicrobial stewardship programs and guidelines in healthcare institutes.

Fang et al. conducted a cross-sectional study of the China Family Panel Studies to examine a gender phenomenon with respect to sports participation. It has been reported that women have more constraints to engage in sports than their male counterparts due to time, knowledge, and interest (6). The authors found that women who were of a high economic status and education level, unmarried, and knowledgeable about the benefits of physical activity were more likely to engage in sports than women who are overweight or are experiencing a chronic disease. In addition, women in the 50–59 age group reported having more time to engage in sports compared to younger women who are busy with attending school, family, and work. Due to the reported health benefits from engaging in physical activity (7), the authors recommend that the Chinese government develop social network policies to support sports participation, alleviate social gender norms and socio-cultural restrictions, improve transportation access to comprehensive sport facilities, and improve social media for sports engagement.

Research by Luo, Song et al. aimed to develop a college student physical literacy questionnaire (CSPLQ) to address the lack of currently available physical activity literacy assessment tools for Chinese college students. The research process of the CSPLQ consisted of two stages: item generation and validation process. Data was collected from seven Chinese colleges and universities. Evidence of content validity was provided for all processes from defining the domain, constructing definitions, generating items for expert review and response processes, content structure analysis, and relationships with other variables. The study was an initial exploratory effort aimed at designing a validated self-report questionnaire on physical activity literacy.

The theme of physical activity is further examined by Luo, Yang et al. who apply Kane's validity framework to evaluate the physical exercise peer support questionnaire (PEPSQ). The article describes the experience of using the framework and considers data related to four inferences (scoring, generalization, extrapolation, implication) that emerge from the assessment process. The findings of the study are interpreted through these inferences. The authors' findings provide evidence for the identification of peer support for physical exercise among Chinese college students. The authors conclude that the key elements that potentially affect college students' participation in physical exercise is an important part of developing health education interventions.

Ishaq et al. aimed to develop the profile and predictors of maternal Quality of Life (QoL) among pregnant women attending a primary healthcare institute in Quetta City, Pakistan. A cross-sectional study was conducted at the Obstetrics and Gynecology Department of Sandeman Provincial Hospital Quetta, Pakistan. Among the respondents, education and household income were positively associated with QoL, yet as the pregnancy progresses, there was a decrease in QoL. The authors recommend that healthcare professionals and policymakers reflect on the identified QoL factors while designing therapeutic plans and interventions for pregnant women.

Shakeel et al. conducted a cross-sectional study in Karachi, Pakistan among obstetricians and gynecologists to examine their knowledge, attitude, and practice of off-label medicine use (OLMU) for female reproductive health issues (FRHI). Although aware of OLMU, most respondents did not follow any guidelines or regulations for OLMU in their hospital due

to liability and risk-to-benefit concerns for the patient. The authors recommend that tailored policies should be established to the local community context to analyze OLMU that addresses patient safety.

Perspectives

By examining concerns about safety, compliance, and distribution through an interdisciplinary approach of public health and history, Caron and Girard Dorsey argue that historical and contemporary mistrust of immunizations which serve to challenge the successful management of a COVID-19 vaccine program in the US should be acknowledged. Unique circumstances surrounding the development of a COVID-19 vaccine, including pressure for rapid production, unclear communication from public health officials, and existing resistance to behavioral protective public health policy measures (e.g., mask-wearing) complicate widespread vaccine adoption. Public health recommendations are offered for the continued management of an effective and safe COVID-19 vaccine and necessary COVID-19 vaccine booster.

Assuring healthy populations during the COVID-19 pandemic and recognizing the role of women researchers in addressing syndemic interactions is the focus of the article by Caron and Aytur. The authors discuss the significance of a syndemic framework which examines the contributions of structural, social, economic, and environmental factors and disease interactions that synergistically act together to contribute to adverse health outcomes (8). The authors describe how the interactions among the social determinants of health (SDoH) and the COVID-19 pandemic have had different results for marginalized populations and have worsened health outcomes for many in this synergistic pandemic. The authors also discuss the role of the exposome, which is the exposure measures for an individual over their lifetime and how those exposures relate to the individual's health (9), and how this concept may help to explain why some populations experience more serious cases of COVID-19 compared to other groups. To respond to this Research Topic, Caron and Aytur also highlight, *via* specific examples, the contributions of female health professionals globally (e.g., chronic disease management, violence prevention, zoonotic transmission) to SDoH and the COVID-19 syndemic, as well as propose health policies to address syndemic-exposome interactions to help mitigate or prevent public health challenges. In particular, the authors call for transformative changes across governments, systems, and infrastructures to support gender-sensitive policies that will improve the SDoH-exposome interactions as key drivers of health.

The perspective offered by Abraido-Lanza et al. about challenges and opportunities experienced by Latina women in academia aligns well with the premise for this Research Topic. The authors analyzed data from the Association of Schools and Programs in Public Health and noted that there are <10% of instructional and tenured faculty in these member programs and schools of public health. This disparity is a form of epistemic oppression which is a type of exclusion that hinders knowledge production and advancement (10). The authors examine this claim by describing national trends on Latina representation in academia, sociopolitical contexts, family-level dynamics, gendered norms, and institutional contexts that impede the full participation of Latinas in academia. Abraido-Lanza et al. propose systemic and organizational reforms necessary to advance the career trajectories of underrepresented scholars. Representative reforms include academic administration being held accountable in establishing, implementing, and evaluating policies for the hiring, retention, and promotion of diverse staff and faculty. Structured mentoring and leadership programs for women can also provide necessary support and guidance.

The perspective offered by Sealy-Jefferson examines racial inequity between Black and white mothers, focusing on several factors accounting for the difference between the two racial groups. The perspective addresses a broad range of determinants responsible for the observed inequitable outcomes for Black people, including maternal health access and quality, maternal mortality, structural racism, mass incarceration, and poverty-stricken living environments. The author also calls for different research questions, orientations, and methodologies in studying injustices in Black maternal health. The author proposes that research questions should not rely on currently available data, or solely on the intellectual curiosity of researchers, but on relevant theories and frameworks and the use of participatory research methodologies for action.

Brief research report

The Cooperative Extension System (Extension) is a US network, in existence for more than a century, that provides community-based education through local Extension offices affiliated with states' land grant universities. Extension education efforts have focused on youth and community development, agriculture, and family and consumer services. Washburn et al. conducted a survey based on the Consolidated Framework for Implementation Research: Intervention Characteristics, Inner Setting, Characteristics of Individuals, and Process to assess the capacity and readiness of policy, systems, and environmental (PSE) change among Family and Consumer Sciences (FCS) Extension agents in Kentucky and Tennessee. Respondents perceived PSE work as valuable while potential barriers reported included perceived complexity, readiness in reporting requirements, and a concern about taking time away from direct education efforts. The authors state that combining PSE work with traditional extension provides research-based, effective programs and interventions to improve and sustain the

health and wellbeing of the communities served is necessary. The authors' findings provide informative insight for other Extension and public health organizations looking to build capacity within community-level educators to improve the population's health.

Study protocol

The evaluation of the efficacy of preconception lifestyle interventions in preventing disease risk factors for a population of overweight and obese women in two Canadian communities, without a history of infertility, and their partners, is the aim of this study protocol developed by Hardy et al. Participants will be randomized to receive the *Healthy for my Baby* intervention or standard care in the preconception period and pregnancy. *Healthy for my Baby* is a novel behavioral intervention developed by the authors to support the adoption of healthy lifestyle habits for women and their partners in preconception and throughout pregnancy. Couples will initiate the preconception intervention by participating in a 60-min motivational interview (MI) session on healthy lifestyle habits. At the end of this session, each member will have set specific SMART (specific, measurable, achievable, relevant, time-bound) lifestyle goals in at least two of five key areas: nutrition, physical activity, sleep, wellbeing (stress, anxiety), and environment (tobacco use, drug use, alcohol consumption, or other toxic substances). Lifestyle goals will be tailored to each participant based on the priorities verbalized in the interview with the aim of improving compliance with Canadian guidelines for diet, physical activity, sleep, and alcohol consumption. Participants will then have access to a mobile phone application designed by the authors that will help them achieve three goals in different dimensions at a time through daily self-monitoring. The study hypothesis is that, compared with standard preconception and obstetrical care, this intervention will lead to an improvement in the lifestyle habits of women and their partners in the preconception period and during pregnancy and a reduction in women's weight in the interval from enrollment to 6 months of follow-up. The primary outcome of the trial is the diet quality of women, assessed with the Canadian Healthy Eating Index (C-HEI) during the preconception period, assessed at baseline, 2-, 4- and 6-months following study enrollment. The secondary objectives of the preconception period include the impact of the intervention on urinary metabolomic indicators of women's dietary exposure, the diet quality of male partners, the other lifestyle habits of women and their partners (physical activity, sleep quality, anxiety, depression, and quality of life), and anthropometric measures of women and their partners (weight, waist circumference, and body fat percentage). After completion of the primary outcome assessment, women and their partners who have achieved a pregnancy within 12 months following enrollment will be followed until the end of the pregnancy. This innovative study will be the first to document the effectiveness of an intervention combining motivational interviews and technology support to improve the lifestyle habits of women with overweight or obesity, without a history of infertility, in the preconception period. Furthermore, it will be the first study to include male or female partners in the evaluation of a preconception intervention.

Systematic review

High rates of maternal mortality due to common preventable causes such as hemorrhage, eclampsia, and sepsis call for safe procedures like Cesarean Section (CS). Although, theoretically, the procedure is intended to protect against adverse maternal outcomes, the increase in cesarean rates in low- and middle- income countries has not been associated with improved perinatal outcomes. In addition to increased risk of neonatal and perinatal mortality in vaginal birth after cesarean (VBAC), previous CS has been reported as being associated with adverse outcomes of subsequent pregnancies such as maternal mortality, blood transfusion, admission in critical care, and hysterectomy. In 2014, the WHO proposed Robson classification for assessing, monitoring, and comparing CS rates within and between healthcare facilities over time. Jamshed et al. meta-analysis assessed women globally according to Robson's classification and reported pooled evidence on the impacts of previous CS on outcomes of subsequent pregnancy. Previous CS was found to be associated with adverse maternal outcomes in subsequent pregnancy and childbirth. The odds of experiencing adverse outcomes for women who experienced repeat-CS was higher than someone who delivered VBAC. The authors found that women who showed pre-eclampsia outcomes were three times more likely to experience repeat-CS than those who delivered VBAC. Women giving birth to their fourth child through CS can be three times more likely to experience pre-eclampsia compared to gravida. This study also revealed that women who have uterine dehiscence as an outcome are more likely to experience repeat-CS than those who delivered VBAC. There were no distinctions in the results between the repeated CS and the VBAC for preterm delivery, heavy bleeding, retained placenta, and maternal death. The authors conclude that the benefits CS can bring to reduce maternal mortality and perinatal outcomes have yet to be realized in low- and middle-income countries.

Community case study

Cholera remains a significant public health problem, especially in Ethiopia, where vulnerable populations live in many resource-limited settings with poor access to safe and clean water and inadequate hygiene practice. Park et al. present a cholera control plan for Ethiopia, including case detection

and reporting, outbreak declaration, case management, and transmission control. Specifically, the authors describe the responsibilities of healthcare facilities and various government levels for a cholera outbreak including the response and control efforts [e.g., oral cholera vaccine (OCV)]. There is a multi-year national commitment to control cholera in Ethiopia despite significant disparity in healthcare service utilization and health outcomes among people at different geographical areas and socio-economic levels. The authors propose recommendations to overcome existing challenges including improving disease surveillance, diagnostics capacity, health information reporting system, effective OCV intervention strategy, community engagement for early case detection and proper case management, and the promotion of water, sanitation, and hygiene is critical. In addition, enhanced surveillance and a comprehensive reporting system will allow the government to assess and evaluate the impact and effectiveness of vaccination when OCVs are pre-emptively used in cholera endemic hotspots or reactively in cholera outbreak settings. Lastly, the authors propose that to better estimate disease incidence, prevalence, mortality rates, and vaccination coverage rates, a multi-sector system is necessary.

Conclusion

The research highlighted herein, addresses this specific Research Topic to demonstrate the many contributions women are making in the field of public health education and promotion globally. General perspectives on a specific field of research inspired and initiated by women; articles celebrating outstanding female researchers and their contributions to public health education; and research studies led by women studying public health education and/or health promotion comprise the Women in Public Health Education and Promotion, 2021, collection.

Author contributions

RC led the planning and writing of the editorial. All authors contributed to the writing and review process for the editorial.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STUDY PROTOCOL
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Healthy for My Baby Research Protocol- a Randomized Controlled Trial Assessing a Preconception Intervention to Improve the Lifestyle of Overweight Women and Their Partners

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Background: Preconception lifestyle interventions appear promising to reduce pregnancy complications, prevent adult cardiometabolic diseases, and prevent childhood obesity. These interventions have almost exclusively been studied in populations of obese infertile women. The development of preconception lifestyle interventions targeting a broader population of overweight and obese women without a history infertility and their partners is needed.

Methods: This study is a multicenter open label parallel group randomized controlled trial. Sixty-eight non-infertile women with overweight or obesity in the preconception period and their partners will be recruited from the Sherbrooke and Quebec City regions. The couples will be randomized in a 1:1 ratio to receive the *Healthy for my Baby* intervention or standard care in the preconception period and pregnancy. Women and their partners will be invited to take part in this lifestyle intervention which includes motivational interviews and daily self-monitoring of lifestyle goals through a mobile phone application. The primary endpoint of this study is the diet quality of women during the preconception period, which will be evaluated using the C-HEI 2007 score at baseline, 2, 4- and 6-months following study enrolment. Women's dietary quality will also be evaluated through the measure of urinary biomarkers of habitual dietary intake at baseline and 2 months in preconception, and 24–26 weeks in pregnancy. Additional indicators of women's lifestyle as well as anthropometric measures will be documented in preconception and pregnancy. For the pregnancy period, the main secondary endpoint is the pattern of gestational weight gain. Pregnancy and neonatal complications will also be evaluated. For partners, diet quality, other lifestyle habits, and anthropometric measures will be documented in the preconception and pregnancy periods.

Discussion: This study will evaluate the effectiveness of a low-cost intervention designed to improve diet and other lifestyle characteristics of women in the preconception period who are overweight or obese. If the *Healthy for my Baby* intervention is efficacious regarding dietary measures, larger trials will be needed to evaluate the impact of this intervention on the rates of pregnancy complications, childhood obesity, and adult cardiometabolic disease.

Clinical Trial Registration: clinicaltrials.gov (NCT04242069).

Keywords: preconception care, pregnancy, overweight and obesity, lifestyle intervention, health technology, randomized controlled trial, biomarkers/urine, metabolomics

INTRODUCTION

The Obesity Epidemic

Overweight and obesity are major risk factors for non-communicable diseases (1) and became pandemic worldwide at the end of the 20th century (2). In the early 2000's, the World Health Organization (WHO) recognized the importance of preventing obesity in order to improve the health of populations (3). Increasing physical activity and improving diet quality are major goals of the 2013 *Global Action Plan for the Prevention and control of Non-communicable Diseases* (4) and should help reduce the prevalence of overweight and obesity. Despite these efforts, global adult obesity rates have nearly tripled from 5 to 15% between 1975 and 2016. Obesity rates are alarmingly high in Canada and the United States where 30 and 38% of adults are obese, respectively (5). Most strikingly, childhood obesity rates have increased by more than 700% during this period, and continue to climb rapidly in Africa and South-East Asia (5). Given the inefficacy of current strategies aimed at preventing adult and childhood obesity, new intervention strategies are urgently needed.

Lifestyle Interventions in the Preconception Period

In the effort to prevent obesity across the life course, interventions in the preconception period appear particularly promising (6). Helping women with overweight or obesity to improve their metabolic health in the preconception period has the potential to diminish pregnancy complications, to improve the long-term cardiometabolic health of these adults, and to prevent childhood obesity of their offspring.

Women with overweight or obesity who enter pregnancy are at increased risk of several complications including gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), fetal macrosomia, and delivery by cesarean section (7). These women are also more likely to gain excessive gestational weight (8), which is an independent risk factor for macrosomia and delivery by cesarean section (9). Several lifestyle intervention studies targeting women with overweight or obesity have been conducted in pregnancy, but they have failed to demonstrate a significant effect on excessive gestational weight gain or maternal and neonatal complications. The results of a recent individual patient data meta-analysis demonstrated that antenatal diet and physical activity interventions are associated with a modest reduction in both gestational weight gain and cesarean section rates, but do not have a significant impact on any other maternal or neonatal outcomes (10). Observational data from a Canadian cohort of over 200,000 pregnant women revealed that for each 10% decrease in maternal pre-pregnancy body mass index (BMI), pregnancy complication rates are lower by more than 10% (11). It is therefore plausible that a preconception intervention aimed at improving the lifestyle habits of women with overweight or obesity could help reduce pregnancy complications through direct impacts on metabolism, weight loss, and the prevention of excessive gestational weight gain. This hypothesis is further supported by evidence from post-bariatric surgery cohorts, which demonstrate a complete reversal of obesity-associated pregnancy complications after weight loss (12).

Intervening to improve the lifestyle habits of women with overweight or obesity and their partners in the preconception period could also prevent the increase in body weight associated with parenthood and improve the long-term metabolic health of adults. Indeed, women and men who become parents are more likely to gain weight and increase their BMI than their childless counterparts (13–15). Furthermore, parity is a risk factor for becoming overweight in non-smoking women (16), and the transition to overweight is partially predicted by excessive gestational weight gain (17). The preconception period thus appears as a promising intervention window to prevent adult overweight and obesity.

Lastly, lifestyle interventions targeting women with overweight or obesity and their partners in preconception could help prevent the transgenerational transmission of overweight and obesity. The transmission of an increased risk of overweight and obesity from parents to their children has been well-documented (18, 19), and several mechanisms have been proposed to explain this phenomenon including metabolic disturbances during gamete formation and fetal life, mitochondrial DNA, epigenetics, microbiota, non-coding RNAs in seminal fluid, and shared behaviors (20–22). The potential impacts on offspring health of a lifestyle intervention targeting couples with overweight or obesity in preconception are 2-fold. From a biological stance, allowing women with overweight or obesity to adopt healthy habits prior to pregnancy could restore a normal metabolic environment for the critical period of embryo programming. According to the theory of the Developmental

Origin of Health and Disease (DOHaD), the restoration of a normal metabolic environment must already be in place in the early first trimester for the future child to be protected against metabolic disease through epigenetic changes (23). Healthy habits adopted prior to pregnancy could also prevent excessive gestational weight gain which is an important mediating factor for the risk of childhood overweight and obesity (24, 25). From a behavioral perspective, encouraging women and their partners to adopt healthy habits prior to pregnancy may increase the likelihood that children will be brought up in an environment where healthy eating, physical activity, sleep, and mental health are embodied (26, 27). In this regard, including male partners in preconception interventions is crucial, since the weight status and lifestyle habits of the fathers has been closely correlated with that of their child (28–30).

The Dearth of Evidence on Preconception Interventions

Several preconception lifestyle interventions have been developed using telephone coaching, face-to-face coaching, motivational interviews, and information technology and are being evaluated in ongoing clinical trials (31–33). Only one randomized controlled trial with published results has evaluated the effectiveness of a lifestyle intervention targeting non-infertile women with overweight or obesity in preconception, and none have included women's partners (34–36). In the preconception arm of the RADIEL trial (37), 228 women at high risk of GDM (with a personal history of GDM or a BMI $\geq$ 30) were randomized to standard care or a lifestyle intervention consisting of advice on diet and physical activity provided through personalized in-person meetings every 3 months. This study did not show a difference in the incidence of GDM between the control and intervention groups. However, these negative results could at least partially be explained by the higher pregnancy rates amongst women with obesity in the intervention group (52% of pregnant women were obese in the intervention group compared with 33% in the control group), which rendered the groups imbalanced when considering pregnancy outcomes (38).

Given the high burden of overweight and obesity on public health and the promising potential of lifestyle interventions targeting couples with overweight or obesity in preconception, further research is needed to elaborate and evaluate such interventions. The aim of this paper is to report the rationale and methods for the *Healthy for my Baby* trial, a randomized controlled trial evaluating the effectiveness of an intervention combining in person contacts with an information technology (IT) support to improve the lifestyle habits of women with overweight or obesity in preconception. This protocol is written in alignment with the 2013 SPIRIT statement (39). The SPIRIT checklist for this clinical trial is provided in **Supplementary File 1**.

Hypothesis

Healthy for my Baby is a novel behavioral intervention developed by our research team to support the adoption of healthy lifestyle habits for women with overweight or obesity, and their partners, in preconception and throughout pregnancy. Our hypothesis is that, compared with standard preconception and obstetrical care, this intervention will lead to:

- An improvement in the lifestyle habits of women and their partners in the preconception period and during pregnancy.
- A reduction in women's weight in the interval from enrolment to either (a) occurrence of a pregnancy or (b) in the absence of pregnancy, 6 months of follow-up.

Among women who achieve pregnancy, we also aim to generate preliminary data on the effect of the intervention on the proportion of women who adhere to gestational weight gain guidelines as well as on rates of complications in pregnancy and the neonatal period.

METHODS AND ANALYSIS

Objectives

In accordance with the Obesity Related Behavioral Intervention Trials Consortium model for the development and evaluation of interventions, the primary aim of this study is to determine the impact of the intervention on disease risk factors (40). This trial will be conducted in two phases. The preconception phase will evaluate the impact of the intervention on preconception risk factors for pregnancy, neonatal, and metabolic complications, which include lifestyle habits and anthropometric measures. These outcomes will provide an insight on the mechanisms through which the intervention might improve clinical outcomes. The pregnancy phase will evaluate whether the intervention has a sustained impact on lifestyle habits, and will allow us to obtain preliminary estimates of potential impacts on clinical maternal and neonatal outcomes.

The primary outcome of the trial is the diet quality of women, assessed with the Canadian Healthy Eating Index (C-HEI) during the preconception period, as it is sensitive to change and has been identified as an independent predictor of gestational diabetes, hypertensive disorders of pregnancy, birthweight, and neonatal fat mass (41–44). This outcome is also associated with parallel changes in other behaviors, such as physical activity, sleep, well-being and environment, which are however less sensitive to change over a relatively short period. Since this trial is the initial evaluation step in the evaluation of a novel intervention, we have chosen to base the power of the trial on this disease risk factor, with all other outcomes being secondary at this point.

We set the maximum duration of preconception follow-up at 6 months as fertility rates tend to plateau or decline after 6 months of attempting to achieve pregnancy (45).

For the Preconception Period:

- The primary objective of this trial is to evaluate the impact of the intervention on the diet quality of women measured with the Canadian Healthy Eating Index at 2, 4, and 6 months of follow-up.
- The secondary objectives of the preconception period are to evaluate the impact of the intervention on:
  - Urinary metabolomic indicators of women's dietary exposure at 2 months follow-up,

  - The diet quality of male partners at 2, 4, and 6 months follow-up,
  - The other lifestyle habits of women and their partners at 3 and 6 months (physical activity, sleep quality, anxious and depressive symptoms, and quality of life),
  - The anthropometric measures of women and their partners at 3 and 6 months (weight, waist circumference, and body fat percentage), and
  - The proportion of women and partners with a weight loss of at least 5% body weight at 3 and 6 months.

After completion of the primary outcome assessment, women and their partners who have achieved a pregnancy within 12 months following enrolment will be followed until the end of the pregnancy. Although, there is a potential for unbalanced study groups if the intervention has an impact on fertility, this exploratory follow-up phase will provide preliminary data on the impact of the intervention on lifestyle and clinical outcomes in pregnancy.

For Pregnancy:

- The main secondary objective of this phase is to explore the impact of the intervention on the proportion of women whose gestational weight gain conforms to the guidelines of the *National Academy of Medicine* recommendations (46).
- The other secondary objectives of the pregnancy period are to explore the impact of the intervention on:
  - The trajectory of dietary and lifestyle habits of women and their partners in the first, second, and third trimesters,
  - Women's urinary dietary exposure metabolomic profile at 24–26 weeks of pregnancy,
  - The change in the anthropometric measures (weight, body fat percentage, and waist circumference) of partners between the first and third trimesters,
  - The proportion of partners with overweight or obesity at study enrolment who have a weight loss of at least 5% body weight in the first, second, and third trimesters,
  - Perinatal morbidity indicators (gestational diabetes, hypertensive disorders of pregnancy, gestational age at delivery, delivery mode, birthweight, and neonatal hypoglycemia),
  - Fertility outcomes (viable pregnancy rate, spontaneous abortion rate, and live birth rate).

Women's diet quality will also be assessed based on metabolomic analysis of urinary samples. We will establish a profile of dietary exposure biomarkers, which will be used to compile a metabolite derived diet quality score (47, 48). This exploratory analysis will provide important data to support its use in a future larger multicenter trial.

Exploratory Objectives:

- To evaluate the correlation between women's C-HEI score and the metabolite derived diet quality score in preconception and pregnancy.
- To explore untargeted metabolomic phenotypes within the study population to find associations between metabolism and eating patterns during pregnancy.

Trial Design and Setting

This study is a multicenter open label parallel group randomized controlled trial coordinated at the Research Centre of the Centre hospitalier universitaire de Sherbrooke (CR-CHUS) in Sherbrooke, Quebec, Canada. The Province of Quebec has a population of 8.5 million. In 2014 overweight and obesity rates were 27 and 15% for adult women and 41 and 18% for adult men, respectively (49). Participants will be recruited from the Sherbrooke and Quebec City regions. The obstetrical care of women from Sherbrooke and Quebec City is provided by general practitioners, midwives, and obstetricians in outpatient clinics. The CHUS is a regional tertiary care center where ∼2,800 deliveries are performed annually. The CHU de Québec Université Laval is a regional tertiary center where ∼7,500 deliveries are performed annually at two sites, the Centre Hospitalier de l'Université Laval and the Hôpital Saint-François d'Assise.

An explanatory design has been chosen to rigorously evaluate the potential benefits of the *Healthy for my Baby* intervention (50). Masking of the research team and participants to the intervention will not be possible given the nature of the study. Couples will be randomized to the intervention or control group in a 1:1 ratio. The randomization list was generated independently by the CRCHUS' biostatistics service using a computerized unstratified blocked randomization with blocks of random sizes 2–6. The group allocation sequence was sent directly to the mobile application programming team who input it into the mobile application software. The mobile application website is hosted on the PIERCE server, a secured research platform developed by the local CRED medical informatics working group. Once participants have provided written consent, completed the trial enrollment form, and completed baseline assessment, their mobile application profile will be created by the research assistant which will trigger randomization to a treatment group. Participants will receive the result of their group allocation by email with a link to install the appropriate version of the mobile application.

Eligibility Criteria and Recruitment

Women in the preconception period will be considered for enrollment if they meet the following eligibility criteria. Inclusion criteria: (1) Age 18 to 40 years old, (2) BMI $\geq$ 25 kg/m^2, (3) the participant intends to conceive within 12 months of trial enrollment, (4) access to a smart phone. While participation of the woman's partner will be strongly encouraged, it is not mandatory for inclusion in the study. Women attempting to conceive by insemination without a history of infertility and same sex partners are also eligible for trial inclusion. Exclusion criteria applicable to all participants: (1) anticipate move to another region, (2) insufficient knowledge of French or English, (3) personal history of infertility. Exclusion criteria applicable to women only: (4) type 1 or 2 diabetes mellitus, (5) prior bariatric surgery, (6) active eating disorder established by clinical diagnosis, (7) medical contraindication to pregnancy, (8) medical

contraindication to physical activity, (9) known or anticipated disease or surgery likely to cause an important weight loss. For exclusion criteria 7, 8, and 9, the physician overseeing the day-to-day operations of the study (IH) will individually review the participant's medical history to determine if they present one of these conditions. If a multiple pregnancy occurs, study follow-up will be stopped to limit potential confounders.

Recruitment of eligible volunteers from the Sherbrooke and Quebec City region began in June 2021 and should be completed within 24 months. Potential participants will be approached by their care provider in general practice and obstetrics and gynecology clinics, or at the emergency department after a spontaneous first trimester abortion. Potential participants will also be approached through advertising on social media and in community drugstores. Postpartum women according to hospital archives will be sent mail invitations to participate in the study at the time that they are considering another pregnancy. If these strategies are ineffective, a list of women who are 6 months postpartum will be obtained from the hospital archives and these women will be sent reverse contact authorization forms through the mail. Women who do not return the form within a month will be considered to have consented to be contacted by the research team.

Interventions

Intervention Arm

Participants randomized to the intervention group will receive the *Healthy for my Baby* intervention. This intervention is based on the Control Theory, according to which behavior can be regulated by engaging oneself in an active process centered on establishing and following-up specific goals (51). Couples will initiate the preconception intervention by participating in a 60-min motivational interview (MI) session on healthy lifestyle habits (52). At the end of this session, each member of the couple will have set specific SMART lifestyle goals (53) in at least two of five key areas: nutrition, physical activity, sleep, well-being (stress, anxiety), and environment (tobacco use, drug use, alcohol consumption, or other toxic substances). Lifestyle goals will be tailored to each participant based on the priorities verbalized in the motivational interview with the aim of improving compliance with Canadian guidelines for diet, physical activity, sleep, and consumption of alcohol (54, 55). Participants will then have access to a mobile phone application designed by our research team that will help them achieve three goals in different dimensions at a time through daily self-monitoring (**Supplementary Figure 1**). Self-monitoring has been shown in a meta-regression analysis to be the most effective behavior change strategy to improve diet and physical activity (56). In addition to allowing participants to track their lifestyle goals, the mobile application includes references on healthy habits for preconception and pregnancy, a research visit calendar, a fertility tracker, links to videos on different aspects of parenthood, and a platform to contact the research team.

One month after enrolment, couples will participate in a second 30-min MI to reevaluate their objectives and help resolve potential obstacles. They will also be invited to set new SMART goals in three of the five key areas. Participants will continue to have access to the mobile application for the remainder of the preconception follow-up. The research team will have access to the information entered in the mobile application and will use this data to determine if the intensity of the intervention needs to be increased. Participants who successfully reach their lifestyle goals will not have any further in-person meetings in the preconception period. Those who fail to meet their lifestyle goals will be contacted for further support and will be invited to participate to a maximum of two additional monthly motivational interview sessions by videoconference. Participants will have the option to track their weight in the mobile application and will be contacted for further support if weight gain is reported. Several reminders have been embedded in the application to improve adherence to the intervention. The research team will also be able to detect participants who are not using the application on a regular basis to contact them for further support.

If the woman becomes pregnant, the application will be put in pregnancy mode and participants will be invited to engage in two additional 30-min MI sessions at 6–8 and 10–12 weeks of gestation. The aim of these additional encounters is both to intensify the intervention in the critical period of early pregnancy and to tailor the lifestyle goals to the symptoms of pregnancy. Participants will keep using the mobile application for self-monitoring throughout pregnancy and up to three additional monthly videoconference meetings will be planned for those requiring further support according to data derived from the application.

Control Arm

Participants randomized to the control group will receive standard advice on healthy lifestyle habits as provided by their usual care provider. Usual care in preconception is the same as that of healthy adults and does not specifically involve access to lifestyle interventions. In the Estrie region, which includes the Sherbrooke area, individuals with obesity, or overweight and a cardiometabolic diagnosis, have access to a free-of-charge program at local health centers, which includes group sessions with a limited individual nutritional intervention. However, these services are neither integrated nor targeted at preconception care and are rarely used by these couples. Participation in these sessions, or in any other lifestyle programs or consultations with a lifestyle professional will be documented. In addition to routine obstetrical care, women with GDM are typically followed by a nutritionist, and those who present comorbidities such as hypertension or morbid obesity may be followed by a nutritionist. Participants in this group will have access to a simplified version of the mobile application containing only the research visit calendar, the fertility tracker, videos on parenthood, and the platform to contact the research team. This version of the application does not contain any information on healthy lifestyle habits.

Participants from both study groups will be allowed to participate in the existing local *Taking Care of your Health* educational program if they are eligible or to consult any health care professional if clinically required. However, they will

be asked not to voluntarily begin a similarly intense lifestyle program during the trial.

Variables and Data Collection

Participants' medical history and socioeconomic status will be evaluated at baseline. Women and their partner's diet quality will be measured with 24-h dietary recalls at baseline, 2, 4, and 6 months in preconception and at 6–8 weeks, 24–26 weeks, and 32–34 weeks in pregnancy. Women will provide urinary samples for the metabolomic analysis at baseline and 2 months in preconception and at 24–26 weeks in pregnancy. Women and their partner's other lifestyle indicators (physical activity, sleep, anxious, and depressive symptoms, quality of life, and attitude toward behavior change), and anthropometric outcomes will be evaluated at baseline, 3 and 6 months in preconception and every trimester in pregnancy. Information on pregnancy and neonatal outcomes will be collected from participants' medical records at the end of the study. The study variables, measuring tools, and the timing of data collection have been summarized in **Table 1**.

Lifestyle Habits

Diet Quality

Diet quality will be measured using the *Canadian Healthy Eating Index* 2007 (C-HEI 2007) which is a 100-point score adapted from the American HEI-2005 to measure adherence to the 2007 Canadian Food Guide (57, 58). The C-HEI 2007 score will be measured at baseline, 2, 4, and 6 months in preconception and each trimester in pregnancy with the *R24W*, an online 24-h dietary recall tool available in French and English, and validated for both pregnant and non-pregnant individuals of the French-Canadian population (59, 60). Three dietary recalls will be used to compile the C-HEI score at each time point, two recalls of weekdays and one recall of a weekend day. On the day the 24-h recall is to be completed, an e-mail will be sent to the participant. If the participant fails to complete the R24W, subsequent e-mails will be sent, within 3 weeks (or within the trimester), until three R24W are completed. Detailed reports of energy, macro and micronutrient, are automatically derived from the recall and will also be compiled and analyzed. Furthermore, a new diet quality index reflecting the 2019 Canadian Food Guide might become available to assess diet quality and will be reported if applicable.

Women's urinary dietary exposure biomarker profiles will be analyzed as a secondary assessment of diet quality. A crossover randomized controlled trial published in 2017 demonstrated that urinary metabolic profiling is a precise tool to evaluate dietary intake of the preceding 72 h, that it is sensitive to change, and that it correlates well with the DASH dietary index (61). Participants will collect urine samples on three random days over 1 week at the designated time frame. These spot samples will be pooled after normalizing using refractive index measurement to guide dilution. Around 40 metabolites will be targeted for the quantitative measurement of dietary intake biomarker concentrations. The concentration of dietary intake biomarkers will be measured using Multiple Reaction Monitoring (MRM) methods on a Triple Quadruple LC-MS/MS instrument (47). Each metabolite can be associated with the consumption of a specific food. These foods will then be grouped together into Healthy Eating Index categories to compute a relative dietary quality score (48).

Physical Activity

Physical activity behavior will be assessed at each research visit using the *International Physical Activity Questionnaires* (IPAQ) (62).

Active Minutes and Step Count

The minutes of moderate to intense physical activity and the daily step count will be measured after each research visit using a 7-day Fitbit recording (Flex 2 model). The use of the Fitbit monitor to measure these variables has been validated both in the general (63, 64) and pregnant population (65).

Sleep Quality

Sleep quality will be evaluated after each research visit using the *Pittsburgh Sleep Quality Index* (PSQI) (66).

Anxious and Depressive Symptoms

The intensity of anxious and depressive symptoms will be evaluated at each research visit with the *Hospital Anxiety and Depression Scale* (HADS). Both the anxiety (HADS-A) and depression (HADS-D) dimensions of this scale have been extensively validated in the general (67) and gynecological population (68). This questionnaire can also be utilized as a screening tool for anxious and depressive disorders with a cut-off value of 8 or greater on the HADS-A or HADS-D subscales (67, 68).

Quality of Life

Quality of life will be evaluated at each visit using the SF-12, a shortened version of the SF-36 which evaluates both physical and mental health and has been validated in the gynecological population (69).

Attitude Toward Behavior Change

The readiness, conviction, and confidence of study participants to change their diet and physical activity will be measured using a 22-item questionnaire. This questionnaire was designed for previous studies (70, 71) at our center and is based on Prochaska and DiClemente's transtheoretical model of change (72).

Anthropometric Measures

All anthropometric measures will be performed by a research assistant who has been trained in these measures based on WHO standards (73).

Pregnancy Outcomes

Total Weight Gain in Pregnancy

Total weight gain in pregnancy will be calculated by subtracting the woman's weight at the last attended preconception visit from the last weight recorded before delivery. The last weight recorded before delivery will be obtained from the patient medical record. Trimester specific weight gain velocity will also be calculated based on the weight measured at the research visits. Trimester-specific gestational weight gain will also be computed using

TABLE 1 | Summary of study variables.

		Timing of data collection in preconception (months)					Timing of data collection in pregnancy (weeks of amenorrhea)			
Variables	**Measuring Tool**	**0**	**2**	**3**	**4**	**6**	**6-8**	**24-26**	**32-34**	**End of study**
Medical history	Homemade questionnaire	•								
Socioeconomic status	Homemade questionnaire	•								
Lifestyle habits										
Diet quality	C-HEI 2007 score measured with the R24W	•	•		•	•	•	•	•	
Diet quality	Urine dietary exposure biomarker profile	♀	♀					♀		
Physical activity	IPAQ	•		•		•	•	•	•	
Active minutes and step count	7-day Fitbit recording	•		•		•	•	•	•	
Sleep quality	PSQI	•		•		•	•	•	•	
Anxious and depressive symptoms	HADS	•		•		•	•	•	•	
Quality of life	SF-12	•		•		•	•	•	•	
Attitude toward behavior change	Homemade questionnaire	•		•		•	•	•	•	
Anthropometric measures										
Height	Stadiometer	•								
Weight	Calibrated scale	•		•		•	•	•	•	
Body fat percentage	Foot to foot bioimpedance	•		•		•	♂	♂	♂	
Waist circumference	Measuring tape	•		•		•	♂	♂	♂	
Pregnancy outcomes										
Last weight before delivery	Patient medical record									♀
Gestational diabetes	Patient medical record									♀
Hypertensive disorder of pregnancy	Patient medical record									♀
Gestational age at delivery	Patient medical record									♀
Delivery mode	Patient medical record									♀
Neonatal outcomes										
Birthweight	Patient medical record									♀
Neonatal hypoglycemia	Patient medical record									♀
Fertility outcomes										
Clinical pregnancy rate	Patient medical record									♀
Spontaneous abortion rate	Patient medical record									♀
Live birth rate	Patient medical record									♀

•*: Evaluated for both partners.* ♀ *and* ♂*: Evaluated for the woman attempting pregnancy or partners only, respectively.*

previously described methodology (74). Both total and trimester specific weight gain will be compared to the NAM recommendations (46).

Pregnancy Complications

The diagnoses of gestational diabetes or hypertensive disorders of pregnancy, gestational age at delivery, and delivery mode will be compiled from women's medical records based on *International Classification of Diseases-Tenth Revision* codes.

Neonatal Outcomes

The birthweight, and the presence of hypoglycemia will be compiled from the newborn medical records.

Fertility Outcomes

The clinical pregnancy rate, spontaneous abortion rate, and the live birth rate will be compiled from the patient medical records.

Participant Timeline

The participant timeline has been summarized in **Figure 1**.

Sample Size Calculation and Analysis Plan

Sample Size Calculation

Since no minimally clinically important effect size has been defined for the HEI score, our effect size has been estimated as a plausible effect of the intervention based on the preliminary results of the *Obesity Fertility* trial (71), which demonstrated a 12.5 ± 13.0 points increase in the average HEI score of women with obesity and infertility after a 6-month lifestyle intervention (unpublished data). An increase of 12 points in the average HEI score was also observed in breast cancer survivors with obesity who received a 6-month dietetic intervention (75). To detect a 10% difference in the average HEI score between groups with a 13-point standard deviation, an alpha value of 5% and 80% power, we will need to recruit 27 women per group (76). To account for a 20% attrition rate (77), a total of 68 women and their partners will be recruited.

Statistical Analysis Plan

Study results will be analyzed at the end of the trial following intent-to-treat principles. Participants' baseline characteristics will be reported to assess group comparability at baseline in preconception and at the beginning of pregnancy. A statistical significance threshold of 5% will be used for all analyses. Statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS version 26) and R (Version 4.0.2) software. No interim analysis will be performed.

Primary Outcome Analysis

Our primary endpoint is the difference in the evolution of the HEI score between study groups in time, which will be assessed using a mixed linear model of the HEI score integrating the effects of time as a continuous variable, study group, and the interaction between the study group and time. This statistical model has been chosen because it will allow us to account for (1) the different lengths of preconception follow-up that will arise as a result of women becoming pregnant throughout the study; and (2) variable timing and number of the *R24W* questionnaires performed by the participants (due to non-adherence to the protocol) (78). The average HEI score in each group at 2, 4, and 6 months will also be compared using standard mixed-model repeated measures ANOVA with *post-hoc* Student's *t*-tests with Bonferroni correction for multiple comparisons. As a secondary analysis, Kaplan-Meier survival curves of women who have increased their HEI score by 10 points or more will be produced, with censoring for dropout or occurrence of pregnancy.

Secondary Outcome Analysis

For the main secondary outcome for the pregnancy phase of the trial, we will use a Chi-squared test to compare the proportion of women who have an adequate gestational weight gain in each group.

For the targeted analysis of urine biomarkers, the concentration of around 40 metabolites will be compared between baseline, 2 months in preconception and 24–26 weeks of pregnancy using repeated measures ANOVA or Friedman test with a Bonferroni adjustment for multiple comparisons. The correlation between the metabolite derived diet quality score and the C-HEI score will be evaluated using Pearson's correlation.

Although our sample size is fairly small, an exploratory multivariate analysis of non-targeted metabolome profiles will be realized using both unsupervised 'natural clustering' analysis and Supervised Random Forest classification.

For the other secondary outcomes, continuous variables will be assessed using Student's *t*-tests or Mann-Whitney tests as appropriate. Dichotomic variables will be analyzed using Chi-squared tests or Fisher's exact test as appropriate.

For participants who achieve a pregnancy prior to the 2-month food recall and/or 3-month preconception visit, lifestyle and anthropometric outcomes at the first pregnancy visit will be used to complete the preconception analysis. Women will be able to signal the occurrence of a pregnancy through the mobile application as soon as a period is missed. The application software will immediately notify the research team which will allow completion of data collection prior to the occurrence of significant pregnancy symptoms such as hyperemesis.

Retention Strategies

Participant retention is critical in all randomized controlled trials and may be even more important in open-label trials where differential attrition of study participants can occur and severely compromise the study results. Several strategies derived from a meta-analysis and expert recommendations have been put in place in order to improve the retention of study participants in this trial (79, 80) including thorough counseling of potential participants before enrolment, creation of a strong study brand, use of technology to ease the burden of participation (research calendar embedded in the mobile application, online dietary recalls with the R24W, email recalls), and flexible hours for study visits. Complementary healthy snacks and drinks will be offered at each study visit and parking fees will be assumed by the research team. After each research visit, participants will gain access to a new video through the mobile application, which will serve as a non-financial participation incentive. These videos have been created in collaboration with a local research team and provide scientifically accurate information on various aspects of parenthood. A fertility planner has been integrated in the mobile application as another non-financial participation incentive. Monetary compensations for time or travel will not be provided for this trial.

Safety Monitoring

In order to document the safety of the *Healthy for my Baby* intervention, we have chosen to follow expert recommendations (81, 82) and implement a comprehensive adverse event monitoring strategy. Monitored adverse events include subjective anxious or depressive symptoms, a score of 8 or higher on the anxiety or depression subscale of the HADS questionnaire (68), physical trauma related to an increase in physical activity,

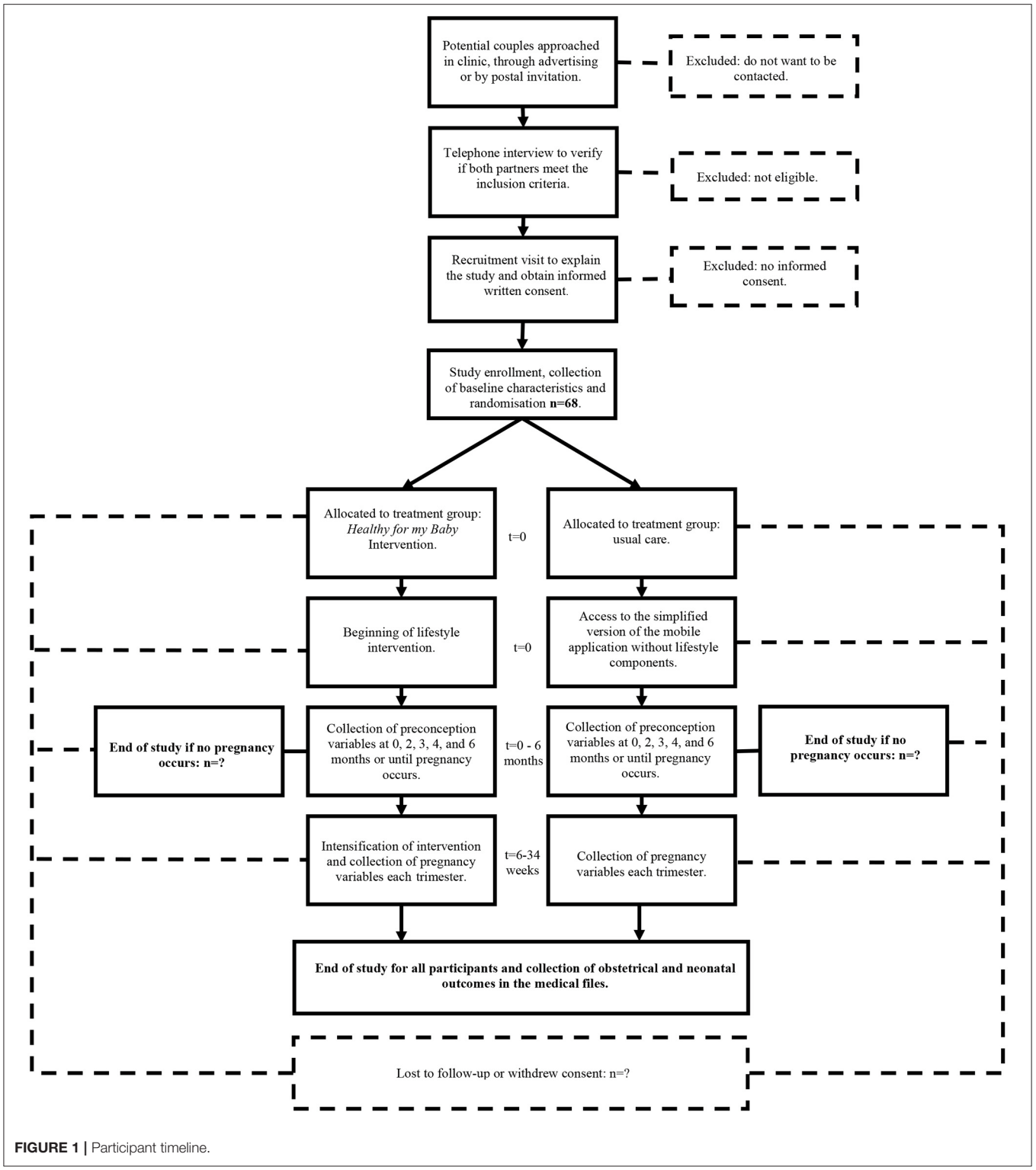

FIGURE 1 | Participant timeline.

placental abruption secondary to a trauma incurred in the context of an increase in physical activity, excessive weight loss on the part of the woman defined as the loss of more than 1 kg per week, intrauterine growth restriction associated with excessive maternal weight loss. These adverse events were defined based on plausible consequences of the intervention because no specific adverse events have been reported in association with lifestyle weight loss interventions (83). All adverse events will

be reported to the DSMB, which will meet every 6 months or more often if needed, to evaluate the nature and rate of adverse events and determine their association with the intervention. If a severe adverse event occurs (requiring hospitalization, causing long-term morbidity, or death) the DSMB and local ethics board will be immediately notified to evaluate the need for trial interruption. No study termination criteria have been defined a priori.

DISCUSSION

This innovative study will be the first to document the effectiveness of an intervention combining motivational interviews and IT support to improve the lifestyle habits of women with overweight or obesity without a history of infertility in the preconception period (34, 35). Furthermore, it will be the first study to include male or female partners in the evaluation of a preconception intervention (36). In addition to documenting the impact of the intervention on the lifestyle habits and anthropometric indices of partners, this analysis will provide insight on the impact of sex and gender in the response to interventions, and will allow us to explore whether the participation of both members of the couple is of added benefit for the achievement of lifestyle goals by each participant.

The body of evidence produced in this trial will be useful to guide future research endeavors on obesity prevention in preconception and pregnancy. This study will document the impact of the intervention on nutritional behaviors in preconception and will provide evidence regarding the plausibility of an effect of the intervention on health outcomes in the preconception period and pregnancy. If the intervention produces positive dietary changes which are sustained through the preconception period and pregnancy, a larger trial will be warranted to assess the effects of the intervention on clinical outcomes of pregnancy.

The use of urinary metabolomic profiling will also allow us to explore possible associations between epidemiological measures of diet and biological (metabolomic) indictors that may reflect dietary changes produced by the intervention. This profiling appears particularly promising as it is an objective means of evaluating dietary intake and is not subject to recall bias. If the metabolite derived diet quality score can be correlated with the C-HEI both in preconception and pregnancy, urinary dietary exposure biomarkers could be used as the sole measure of dietary intake and quality in future studies.

We will also document several measurements of the feasibility of targeting couples with no history of subfertility in the preconception period including recruitment rates, attrition rates, effective recruitment and retention strategies, and pregnancy rates within a 12-month preconception period. No similar study has been registered on the platforms clinicaltrials.gov or on the International Clinical Trials Registry Platform.

The methodology of this trial presents several strengths. Firstly, our intervention was designed to be in line with both the UK Medical Research Council statement on the development and evaluation of complex interventions, and the Consort statement for the reporting of non-pharmacologic interventions (84, 85). Indeed, our intervention is based on a recognized behavior change model, specific intervention targets have been outlined, and the behavior change techniques at play have been well-described. These elements will improve the likelihood of intervention success and allow replication of the intervention if it is proven to be effective. Secondly, we have chosen to document the effectiveness of the intervention on metabolic risk factors in the preconception period prior to conducting a large clinical trial with sufficient power to detect differences in clinical outcomes. This first step in evaluating a complex behavioral intervention is in line with the Orbit recommendations (40) and will avoid a waste of resources if the intervention appears to be ineffective. This will also avoid the limitations in outcome assessment found in the RADIEL trial (38), where the measure of the primary outcome in pregnancy, when randomization took place in preconception, severely compromised the validity of the results. Thirdly, the choice of an explanatory randomized controlled trial design will provide good internal validity to document the effects of the intervention. Lastly, our methodology includes a detailed and systematic approach to recruitment, retention, and adverse event monitoring which will all contribute to the validity and success of the study.

This study presents several limitations. First, our choice of diet quality in preconception as our primary endpoint, which is an intermediate variable for clinical outcomes, will limit the direct relevance of this study for clinical practice. Diet quality in preconception is also controversial, as two large cohort studies have reported that adhering to a combination of healthy habits including high diet quality, physical activity, being a non-smoker, low stress, and a normal BMI is more protective against the occurrence of GDM than any one of these factors alone (86, 87). However, for the purposes of sample size calculation, a single primary outcome had to be chosen and diet quality appears as the most predictive of pregnancy outcomes and is more sensitive to change (41–44, 58). Second, given the nature of the intervention, the masking of participants and the project coordination team to the study group will not be possible. Diet quality will be measured through an online 24-h dietary recall and urine samples, and the other lifestyle habits scores will be collected with the use of self-reported questionnaires to limit social desirability. Lastly, the strict selection of study participants could induce a selection bias and will limit the external validity of this trial. To limit this potential bias, we will use various recruitment methods to contact participants from diverse socioeconomic and cultural backgrounds and the baseline characteristics of participants in each group will be reported with our results.

We report the rationale and methods of an innovative randomized controlled trial evaluating the effectiveness of a low-cost intervention to support adoption of healthy lifestyle habits for women with overweight or obesity in the preconception period. This study will provide useful information on the feasibility of preconception trials, and on the potential of preconception interventions to prevent complications of overweight and obesity. This study will also help establish whether urinary metabolomic profiling can be used as a reliable and objective measure of diet quality in preconception and

pregnancy. If the *Healthy for my Baby* intervention significantly improves lifestyle scores in women with overweight or obesity during preconception, larger trials will be needed to directly evaluate the impact of this intervention on clinical outcomes. Ultimately, if proven effective, this intervention could be integrated in regular clinical practice to help improve the health of couples, pregnant women and their babies. Future large-scale implementation of this intervention in diverse clinical settings will be facilitated by its low cost, ease of use and accessibility.

ETHICS AND DISSEMINATION

This study has been designed to follow the principles of the Canadian Tri-Agency Framework for the Responsible Conduct of Research (88). The approbations of the CHUS and CHU de Québec Université Laval Ethics Committees have been obtained prior to the start of recruitment. Any amendment to this protocol will be communicated to the Ethics Committees and updated on clinicaltrials.gov. All participants will be informed of the benefits and risks of study participation by a member of the research team or a research assistant and provide written informed consent before enrollment. Participants will be able to withdraw from the study at any point without consequences.

Urine samples will be anonymized and identified with the participant's study ID prior to being shipped to Professor John Draper's laboratory at Aberystwyth University. Urine samples will be destroyed after analysis.

Participant data will be de-nominalized and coded in a secured database. The coding key will only be available to the research team in a password-protected file. Study data will be stored for 10 years on a secured server and then destroyed. Study data will not be made publicly available and will only be accessible to the research team.

Study results will be disseminated through presentations at provincial, national, and international conferences and publications in peer-reviewed journals. The results will also be made available to the public through publication on clinicaltrials.gov and partnerships with patient advocacy groups. Presented and published results will not allow the identification of study participants.

AUTHOR CONTRIBUTIONS

IH wrote this manuscript and drafted the tables and figures. WF provided expertise on clinical trial design, complex interventions, maternal fetal medicine, adverse event monitoring, and statistical analysis. J-PB provided expertise in preconception lifestyle interventions, choice of relevant measuring tools, obesity medicine, and statistical analysis. AL provided expertise on urinary metabolomic profiling methods and on the analysis of urinary biomarker concentrations. A-SM provided expertise on the tools, timing, and analysis of nutritional outcomes. FC overlooked the statistical analysis plan. All authors read, edited, approved the final manuscript, and contributed significantly to the design of this clinical trial.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.670304/full#supplementary-material

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Prescribing Patterns for Upper Respiratory Tract Infections: A Prescription-Review of Primary Care Practice in Quetta, Pakistan and the Implications

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Background: To identify and address the potential overuse of antibiotics, it is important to ascertain the prescribing practices of physicians. We, therefore, conducted this prescription analysis to document URTI-specific antibiotic prescription frequency in a public primary healthcare setting of Quetta city, Pakistan.

Methods: A retrospective record review was conducted of all prescriptions for URTIs in Combined Military Hospital, Quetta from 1 March to 31st May 2021. The Mann-Whitney U and Jonckheere–Terpstra test was used to evaluate the association between the tendencies of a different group of prescribers. p-value of <0.05 was of statistical significance.

Results: Over the 3 months, 50,705 prescriptions were screened and analyzed according to the established inclusion and exclusion criteria. A total of 4,126 (8.13%) URTI prescriptions met the inclusion criteria, of which 2,880 (69.80%) prescriptions contained antibiotics. Among all antibiotics, penicillins (Amoxicillin + Clavulanate) were the most prescribed antibiotic, constituting 1,323 (45.9%) of total antibiotics prescribed for all cases, followed by the Macrolide group 527 (18.2%). The Jonckheere–Terpstra test revealed a statistically significant association between the status of the prescriber and the diagnosis ($p = 0.002$). Furthermore, a moderate positive trend was reported with specialists being more competent in antibiotic prescribing based on their diagnosis, followed by postgraduates and house officers ($\tau = 0.322$).

Conclusion: The prescribing patterns for the management of URTIs in the hospital were inconsistent with current guidelines. Strict adherence to guidelines must be ensured and antibiotic prescribing for URTIs should be discouraged.

Keywords: prescribing patterns, upper respiratory tract infections, prescription-review, Quetta city, Pakistan

INTRODUCTION

Upper respiratory tract infections (URTIs) are acute infections involving the nose, paranasal sinuses, pharynx, larynx, trachea, and bronchi (1). Often mild and self-limiting in nature, URTIs occasionally lead life-threatening complications (2). Primarily caused by the Rhinovirus (3, 4), 0.5–10% of the reported cases are because of Group A Streptococci (1). Therefore, physicians must differentiate viral and bacterial pictures while establishing an effective therapeutic plan for patients with URTIs (5). However, defining and differentiating such patients is difficult because the clinical presentations connected with bacterial or viral-related URTIs commonly overlap (6), hence antibiotics are frequently prescribed to manage URTIs in primary care settings (7–11). Nevertheless, and other than certain exceptions, antibiotics are unnecessarily prescribed for URTIs (12). This frequent use of antibiotics adds a burden to healthcare systems that result in clinical failure and/or an increase in the development of antibiotic resistance (13).

The inappropriate and over-prescribing of antibiotics in ambulatory care is frequently reported in the literature (11, 14, 15). Rowe and Linder claimed that most antibiotic use in the US occurs in ambulatory care and 30–50% is inappropriately prescribed to the patients (16). Zhao et al. (17) in their nationwide study also reported inappropriate antibiotic prescribing in China where >50% of the antibiotic prescriptions were inappropriate at the tertiary-level hospitals. Another study revealed that ambulatory care physicians in the US wrote almost 12 million prescriptions for URTIs and acute bronchitis, of these 51% of adults with colds were prescribed an antibiotic, 52% in non-specific URTIs, and 66% in acute bronchitis (18). The hysterical and indiscriminate antibiotic use in ambulatory care has increased the risk of resistance development that is further augmented by their low cost and easy accessibility (18–21). As a result, common infections are now becoming more difficult to treat with standard antibiotics, forcing a shift to newer generations of antibiotics, which are more specific and targeted, but more expensive, and with a higher level of side effects (22–25).

Quality use of antibiotics is getting worse in the Asian region. Antibiotics consumption between the years 2000–2015 increased from 3.2 to 6.5 billion DDDs (103%) in India, from 2.3 to 4.2 billion DDDs (79%) in China, and 0.8 to 1.3 billion DDDs (65%) in Pakistan (26). Routine microbiologic cultures and sensitivity testing is often not performed, antibiotic therapy is empirical, and the few available antibiotics are overused or misused. This increases the emergence and spread of resistance and, therefore sub-optimal clinical outcomes (27, 28). Shifting our concerns to antibiotic use in Pakistan, the country is facing a huge crisis when quality use of antibiotics is discussed in the literature. Augmented by the data supplied by Quintiles-IMS, the Center for Disease Dynamics, Economics and Policy (CDDEP) reported an increasing sales trend and suggested a rise in consumption of almost every antibiotic in Pakistan (29). However, the data covered sales of antibiotics registered for human use only and there is no information about antibiotic use in animals or the agricultural sector. Very recently Bilal et al. (30) reported high resistance to commonly used antibiotics and identified gaps in surveillance and breaches in methodological data. The information was available from only two provinces of the country and no data was available from the other provinces of Pakistan.

Pakistan despite having an essential drug list is facing issues of lacking standard guidelines for the treatment of infectious diseases (31). In Pakistan, data suggest that in tertiary care hospitals junior doctors tend to follow the prescriptions of senior or specialist doctors, yet for them, standard treatment guidelines are non-existent to guide clinical decisions (31, 32). To develop a national antibiotic policy or infection control policy, data on antibiotic prescribing patterns in various infections reporting to different tertiary care public and private hospitals are needfully required.

Correlating irrational use of antibiotics in URTI, large variations in antibiotics prescribed for URTIs exist that are difficult to explain (33). Within this context, the patterns of antibiotic prescription show that it has a huge impact on treatment outcomes (34). However, prescribing an antibiotic is a complex task that requires diagnostic skills, knowledge of antibiotics, understanding of the principles of clinical pharmacology, communication skills, and the ability to make decisions based on judgments of potential benefit and risks, having considered available evidence and specific factors relating to the patient being treated. Prescribing an antibiotic for URTIs is fundamental where the knowledge of physicians with proper training on antibiotics is highly needed. Additionally, factors including patient' age, religious beliefs, comorbidities, adherence to treatment guidelines, and financial status influence the prescribing patterns of antibiotics (35). Therefore, the guide to good prescribing highlights the selection and evaluation of appropriate drug therapy and consider medication cost when prescribing (36). Consequently, prescribing practices play an important role in deciding the success of the therapy and therapeutic outcomes. Consequently, we conducted this prescription analysis to document URTI-specific antibiotic prescription frequency in a public primary healthcare setting of Quetta city, the provincial capital of Baluchistan province.

METHODS

Study Design and Prescription Selection Criteria

A retrospective prescription analysis was conducted whereby all prescriptions from 1st March 2021 to 31st May 2021 were screened and retrieved for further investigation. Prescriptions with mentioned diagnosis of "URTI," "tonsillitis," "pharyngitis," "rhinitis," "common cold," "sore throat," "cough," or "otitis media" were included in the study (1). Incomplete prescriptions, missing diagnoses, or prescriptions with more than one infection were excluded from the study as we wanted to minimize the uncertainty of the diagnosis hence the purpose of prescribed antibiotics.

Identification of URTI Diagnosis

URTIs were defined based on the most agreed criteria (1). All prescriptions were in hard copies, retrieved manually from the

Outpatient Departments (OPDs) of the hospital. Because of the unavailability of symptomatology or laboratory results, the validity of diagnosis was not viable and hence we selected the prescriptions solely on the written diagnosis on the prescription. The prescriptions were screened manually by the first author, who is a qualified and practicing pharmacist and has considerable experience and competence in this regard.

Classification and Appropriate Prescribing of Antibiotics

A comprehensive guideline for the management of Respiratory Tract Infections is provided by the Medical Microbiology & Infectious Diseases Society of Pakistan (37). However, specific instruction on the management of URTIs is not available in Pakistan. Subsequently, we evaluated prescribing practices based on the recommendations of the National Institute for Health and Care Excellence (38). The classification of antibiotics used in this study was adapted from 2019 WHO AWaRe Classification Database of Antibiotics for evaluation and monitoring of use (39).

Study Settings and Sampling

The research was conducted at the Out-Patient Department of Combined Military Hospital (CMH), Quetta. Combined Military Hospital is a tertiary care teaching hospital situated in Quetta Cantonment and is operated by Pakistan Armed Forces. After British colonization, it was established as British Military Hospital (BMH) in 1854, which was converted to the Indian Army Medical Corps (IAMC) in 1927. After partition in 1947, it was handed over to Pakistan Army and was named CMH. Combined Military Hospital is one of the biggest hospitals of the city and in the access of the public. All departments are well established here with facilities and modern machinery.

Statistical Analysis

The data was coded and entered into Statistical Package for the Social Sciences (SPSS), version 21 for further analysis. The Kolmogorov-Smirnov test was used for testing the normality of the sample distribution. Both descriptive and inferential statistics were used for data elaboration. Frequencies and percentages were used to summarize the data. The Mann-Whitney test was used to associate dichotomous variables. The Jonckheere–Terpstra test was used to evaluate the trend of association between the tendencies of a different group of prescribers. Where significant associations were reported, the effect size was calculated by using the Kendall tau correlation coefficient. p-value of <0.05 was of statistical significance.

Ethical Approval

The ethics committee of the Faculty of Pharmacy & Health Sciences, University of Baluchistan, Quetta approved the study. Permission for data collection was also taken from the Commandant CMH, Quetta. Being a record review, consent for publication was not required.

RESULTS

Over the 3 months, 50,705 prescriptions were screened and analyzed according to the established inclusion and exclusion criteria. A total of 4,126 (8.13%) URTI prescriptions met the inclusion criteria, of which 2,880 (69.80%) prescriptions contained antibiotics. Nearly 40% of the prescriptions were diagnosed as non-specific URTI followed by cough (694, 16.8%) and rhinitis (491, 11.9%). Thirty percent of prescriptions were from the pediatrics unit and the majority (1,664, 78.3%) of the prescription with URTIs were prescribed by postgraduates (**Table 1**).

Table 2 presents the frequency of antibiotics prescribed to patients. Among all antibiotics, penicillins (Amoxicillin + Clavulanate) were the most prescribed antibiotic, constituting 1,323 (45.9%) of total antibiotics prescribed for all cases, followed by the Macrolide group 527 (18.2%). In terms of prescribing, most of the patients were prescribed Amoxicillin + Clavulanate

TABLE 1 | Study characteristics by age, prescriber status, and diagnosis.

Characteristics	Number of prescriptions with confirmed URTIs	Number of prescriptions with antibiotics, *N* (%)
Patients' age (years)		
> 10	1,145	951 (83.0)
19-Oct	856	553 (64.6)
20–29	512	385 (75.1)
30–39	687	412 (59.9)
40–49	475	315 (66.3)
50,59	388	224 (57.7)
> 60	63	40 (63.4)
Prescriber status		
House officers	654	514 (78.5)
Postgraduates	2,125	1,664 (78.3)
Specialists	1,347	702 (52.1)
Prescribing OPD		
Family	774	18.8
Pediatrics	1,268	30.7
ENT	402	9.7
General medicine I	727	17.6
General medicine II	558	13.5
General medicine III	397	9.6
Diagnosis		
Non-specific URTI	1,648	39.9
Cough	694	16.8
Sore throat	406	9.8
Rhinitis	491	11.9
Pharyngitis	472	11.4
Tonsillitis	157	3.8
Otitis media	79	1.9
Sinusitis	149	3.6
Nasopharyngitis	30	0.7

OPD, outpatient department, ENT, ears, nose, and throat.

TABLE 2 | Choice of antibiotics prescribed for upper respiratory tract infections.

Antibiotic class	Anatomical therapeutic chemical code	Name of antibiotic	Prescribed for URTI *N* (%)	Prescribed by house officers *N* (%)	Prescribed by postgraduates *N* (%)	Prescribed by specialists *N* (%)
Penicillins	J01CA	Amoxicillin+clavulanate	1,323 (45.9)	57 (4.3)	1,026 (77.5)	240 (18.1)
		Amoxicillin	260 (9.0)	2 (0.7)	251 (96.5)	7 (2.6)
Macrolides	J01FA	Clarithromycin	311 (10.8)	56 (18.0)	157 (50.4)	98 (31.5)
		Azithromycin	198 (6.8)	14 (7.0)	144 (72.7)	40 (20.2)
		Erythromycin	18 (0.6)	8 (44.4)	9 (50.0)	1 (5.5)
Cephalosporins	J01DB/C	Cefixime	459 (15.9)	11 (2.3)	417 (90.8)	31 (6.7)
		Cefaclor	33 (1.1)	0	17 (51.5)	16 (48.4)
Tetracyclines	J01AA	Doxycycline	13 (0.4)	0	8 (61.5)	5 (38.4)
Sulfonamide	J01EE	Co-trimoxazole	20 (0.6)	1 (5.0)	8 (40.0)	11 (55.0)
Quinolones	J01MA	Levofloxacin	185 (6.4)	22 (11.8)	90 (48.6)	73 (39.4)
		Moxifloxacin	40 (1.3)	0	29 (72.5)	11 (27.5)
		Ciprofloxacin	32 (1.1)	8 (25.0)	11 (34.3)	12 (37.5)

after consultations with postgraduates, compared to specialists and house officers respectively.

Among all URTI cases, Amoxicillin + Clavulanate was the most favored antibiotic in more than 50% of cases, except for sinusitis and nasopharyngitis. Levofloxacin was preferred as the treatment of choice in sinusitis (12.1%) while Cefixime was prescribed for Nasopharyngitis (20%). The antibiotic prescription against specific diagnoses is described in **Table 3**.

The Jonckheere–Terpstra test revealed a statistically significant association between the status of the prescriber and the diagnosis ($p = 0.002$). Furthermore, a moderate positive trend was reported with specialists being more competent in antibiotic prescribing based on their diagnosis, followed by postgraduates and house officers ($\tau = 0.322$). No significant association, however, was reported among other study variables.

DISCUSSION

Quality use of antimicrobials and an increased frequency of antimicrobial resistance (40) have emerged as a major health crisis. Antimicrobial resistance has spread to almost all countries and regions, including Pakistan, owing to the indiscriminate use of antibiotics and poor infection control practices. Several factors contribute to the development of AMR and among those irrational prescribing, free availability of antibiotics, and patient-related factors are commonly highlighted in the literature. Within this context, Sulis et al. (40), in their meta-analysis concluded that antibiotics are highly prescribed in primary care and there is a need for urgent action to improve prescription practices, starting from the integration of WHO treatment recommendations and the AWaRe classification into national guidelines. Therefore, the primary objective of the current study was to assess the prescribing practices of physicians while managing patients with URTIs in a primary healthcare setting of Pakistan. Although prescribing practices for URTIs are reported from other parts of Pakistan, the current study is the first piece of evidence reported from the province of Balochistan. Furthermore, our focus was strictly on prescribing practices for URTIs, and that is what we managed to achieve, makes this study different from others as they reported both upper and lower respiratory tract infections.

Our study highlighted frequent use of antibiotics (69.80%) for URTIs from Quetta city, Pakistan, and the published literature provides mixed results in this context. By and large, the prescription rate for URTI in the current study was higher than the rates observed from the Asian region. Antibiotics were prescribed to 51.6% of the patients in Bahrain (40) and 31.8% of patients in Malaysia (11). In Japan, antibiotics were prescribed to 60% of the patients diagnosed with URTIs (41). However, the antibiotic prescribing rate in URTIs in this study was lower than what is reported in other studies. John et al. (42) reported that almost 88% of prescriptions contained antimicrobials for the treatment and management of acute tonsillitis in the UAE. Also, a multi-center study in Pakistan reported that 88.9% of the prescriptions contained antibiotics for the treatment and management of URTIs (43). The differences in rates could be explained by different natures of the denominator used in these studies as well as the study setting, data collection period, and the difference in the types and availability of antibiotics. Additionally, patients' expectations or demands of an antibiotic during the consultation are also frequently reported in the literature as a major reason for inappropriate antibiotic prescribing.

As documented in the literature and guidelines, only a very limited number of patients with URTIs warrant antibiotic treatment (38, 44, 45). However, this study has found antibiotics were frequently prescribed for non-specific URTIs, cough, and rhinitis (**Table 3**). Within this context, The Centers for Disease Control and Prevention (CDC) provides clear criteria for physicians when diagnosing URTIs. The presence of tonsillar exudates, tender anterior cervical adenopathy, history of fever, and lack of cough is an indication that antibiotics are not required under such conditions (46). For that reason, appropriate clinical judgment is fundamental while ascertaining bacterial etiology before antibiotics are prescribed in URTIs. Parallel to this measure, Rezal et al. (11), suggested that developing and

TABLE 3 | Antibiotic prescription against specific diagnosis.

Diagnosis	Cases prescribed with antibiotic (*N*)	Types of prescribed antibiotics					
		Amoxicillin + clavulanate	Amoxicillin	Clarithromycin	Azithromycin	Erythromycin	Cefixime
Non-specific URTI	1,648	579 (35.1)	160 (9.7)	77 (4.7)	108 (6.6)	4 (0.2)	246 (14.9)
Cough	693	156 (22.5)	39 (5.6)	124 (17.9)	26 (3.8)	8 (1.2)	32 (4.6)
Sore throat	406	207 (51.0)	16 (3.9)	18 (4.4)	6 (1.5)	0	19 (4.7)
Rhinitis	491	80 (16.3)	22 (4.5)	12 (2.4)	16 (3.3)	0	59 (12.0)
Pharyngitis	472	166 (35.2)	13 (2.8)	58 (12.3)	25 (5.3)	5 (1.1)	51 (10.8)
Tonsillitis	157	70 (44.6)	2 (1.3)	11 (7.0)	7 (4.5)	1 (0.6)	19 (12.1)
Otitis media	79	28 (35.4)	0	5 (6.3)	0	0	14 (17.7)
Sinusitis	149	33 (2.1)	4 (2.7)	6 (4.0)	6 (4.0)	0	13 (8.7)
Nasopharyngitis	31	4 (13.3)	4 (13.3)	0	4 (13.3)	0	6 (20.0)
Non-specific URTI	1,648	23 (1.4)	3 (0.2)	3 (0.2)	69 (4.2)	5 (0.3)	7 (0.4)
Cough	693	1 (0.1)	2 (0.3)	6 (0.9)	45 (6.5)	17 (2.5)	8 (1.2)
Sore throat	406	0	2 (0.5)	0	12 (3.0)	0	0
Rhinitis	491	4 (0.8)	2 (0.4)	0	12 (2.4)	5 (1.0)	4 (0.8)
Pharyngitis	472	2 (0.4)	2 (0.4)	2 (0.4)	57 (5.7)	5 (1.1)	0
Tonsillitis	157	3 (1.9)	2 (1.3)	0	0	0	6 (3.8)
Otitis media	79	0	0	0	0	3 (3.8)	6 (7.6)
Sinusitis	149	0	0	9 (6.0)	18 (12.1)	5 (3.4)	0
Nasopharyngitis	31	0	0	0	2 (6.7)	0	0

practicing local antibiotic guidelines and continuous medical education regarding antibiotic use also make a huge difference in rational antibiotic prescribing. Using such measures will help make the right medication choices and dosing. Eventually, a successful reduction in antibiotic prescription will result in a rapid drop in AMR. The Australian initiative toward the use of quinolones through its national pharmaceutical subsidy scheme is an excellent example whereby this policy has successfully preserved the utility of this class of antimicrobial drugs for the treatment of most infections (47). The efficiency of practicing guidelines for antibiotic prescribing is also evident in literature whereby by reducing macrolides prescription in Japan, a decline in resistance rate from 22 to <2% of group A streptococcal isolates was reported (48).

The trend of association reported specialists being more competent in antibiotic prescribing based on their diagnosis, followed by postgraduates and house officers. From the clinical perspective, the reported trend is comprehensible. As experience increases, healthcare professionals also expand their skills and knowledge while practicing safe patient care. Also, experienced healthcare professionals are often more prepared mentally and are equipped with proficiency in dealing with a medical crisis. In line with what is being discussed, Lewis et al. (49), in their qualitative study reported that among junior doctors, knowledge, and expertise played a key role in prescribing mistakes. Krishnakumar and Tsopra (50) also mentioned personal factors such as experience and knowledge while choosing a particular antibiotic in clinical conditions. We must remember that antibiotic prescribing is a complex, context-dependent, and dynamic process that entails the balancing of many tensions. Other than that, we also believe that the variations in prescribing between the different prescribers in the current study settings are attributed to some other factors. Where biomedical factors provide key assistance while selecting an antibiotic, factors ranging from attitudes of the prescribers and patients to managerial constraints and policies can also influence the prescribing decision. Our claims are supported by the meta-ethnography published by Wojcik et al. (51) whereby the authors reported that antibiotic prescribing is an intricate phenomenon and comprehensive efforts are needed to promote the distribution of responsibility for antibiotic decisions. Consequently, it is high time that policymakers need to take steps to address these issues. Potential next steps should include continuous medical education for the house officers and implementation of stewardship programs focusing on strict compliance of guidelines implementation.

CONCLUSION

The prescribing patterns for the management of URTIs in the hospital were inconsistent with current guidelines. Quality use of antibiotics can help prevent the emergence of AMR; consequently, a better understanding of appropriate antibiotic prescribing must be fostered among prescribers. Strict adherence to guidelines must be ensured and antibiotic prescribing for URTIs should be discouraged. We also urge the policymakers to introduce antimicrobial stewardship programs and guidelines in healthcare institutes that will help with planning future initiatives among the primary healthcare centers of Pakistan.

LIMITATIONS

In a single-centered study, the generalizability of the findings is always an issue. Also, the diagnoses of URTIs were based

on the written diagnosis on the prescription and we did not verify the accuracy of the clinical examination and diagnosis with the prescribers due to the reasons described earlier. We, therefore, recommend a comprehensive study involving multiple (public and private) healthcare institutes with a confirmed diagnoses of URTI in consultations with the prescribers.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The Ethics Committee of the Faculty of Pharmacy and Health Sciences, University of Baluchistan, Quetta approved the study. Permission for data collection was also taken from the Commandant CMH, Quetta. Written informed consent was not required in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HH, NS, AS, and AR conceptualized and designed the study. FB, SR, QI, and SH collected the data while SU, MM, and AT analyzed and interpreted the data. The study was supervised by AK and FS. All authors have met the criteria for authorship and had a role in preparing the manuscript. Also, all authors approved the final manuscript.

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Challenges, Inquiry, and Recommendations: Effective COVID-19 Vaccine Management in the Face of Public Mistrust and Concern

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By examining concerns about safety, compliance, and distribution through an interdisciplinary approach of public health and history, we argue that historical and contemporary mistrust of immunizations serves to challenge the successful management of a COVID-19 vaccine program in the U.S. Unique circumstances surrounding the development of a COVID-19 vaccine, including pressure for rapid production, unclear communication from public health officials, and existing resistance to behavioral protective public health policy measures (e.g., mask-wearing) complicate widespread vaccine adoption. Currently, the demand for first and second COVID-19 vaccine doses, as well as the COVID-19 booster, continues to fluctuate in the U.S. population as COVID-19 variants continue to emerge. This hesitancy has resulted in a stalled vaccination program and the absence of herd immunity. To support the successful management of a vaccine program, we recommend public health education and communication measures that can be tailored to local community needs while preparing realistic public expectations surrounding the efficacy of a COVID-19 vaccine. A tailored approach may reduce vaccine hesitancy in American society. The perspectives offered herein present a pathway that is applicable to the current COVID-19 vaccine management program in the U.S., other global locations, and future pandemics.

Keywords: COVID-19, vaccine, safety, compliance, distribution

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INTRODUCTION

Absence of realistic expectations about COVID-19 vaccine protection against emerging virus variants and knowledge about potential serious side-effects following vaccine administration could compromise both the public's health and long-term trust in vaccine science. While vaccines have saved numerous lives and often are perceived to be "magic bullets" (Marcotte et al., 2015) against disease, history as well as contemporary events reveal multiple reasons why Americans may mistrust vaccines or hold unrealistic expectations about them. In an environment where public health efforts (e.g., mask-wearing and social distancing) are often rejected by individuals, or where ignorance remains about implementing these defensive measures properly, it is challenging, yet critical, to ensure that the United States (U.S.) administers a COVID-19 vaccine effectively for it to have a substantial role in curtailing the pandemic.

At the beginning of the pandemic, there were considerable supply issues with COVID-19 vaccines. In early January 2021, COVID-19 vaccine demand far outstripped vaccine supply worldwide. The U.S. had a considerable need; hundreds of thousands had died, meaning the U.S. had the highest recorded cases of COVID-19 deaths worldwide. Fortunately, due to heavy investment, the U.S. also quickly had the world's largest stockpile of COVID-19 vaccines. From a conventional perspective, it would be expected that the population would rush to get vaccinated and receive herd immunity. But this was not the case. This disconnect in a country which desperately needed vaccines, had them, and the population refused them needs to be understood, as this pattern appears to be emerging in developing countries. Here, we will examine three issues related to vaccine hesitancy (namely, concern about safety, compliance, and distribution) through an interdisciplinary approach of public health and history. Vaccine hesitancy can be defined as the delay in acceptance of, or wariness about, vaccine effectiveness despite the availability of vaccination services (MacDonald, 2015). Because individuals who are hesitant may accept vaccines eventually, we will focus on this group rather than those who reject vaccines absolutely. This approach will illustrate that successful vaccine administration, regardless of the infectious disease threat, may prove challenging because there are historical as well as contemporary bases, sometimes controversial, for questioning immunizations.

These doubts might be exacerbated by unique circumstances surrounding the COVID-19 vaccine. (Although there are several COVID-19 vaccines and boosters that currently exist, more may be developed. Some may face more scrutiny than others, such as the mRNA-based Pfizer/BioNTech and Moderna vaccines. This article will refer to them all as one COVID-19 vaccine because hesitancy to COVID-19 vaccines, as a whole, is the focus of our work). Overall, a vaccine is likely to evoke public hesitancy by challenging lay behavior, public expectations, and individual rights. To address these challenges to vaccine adoption, we recommend an approach that utilizes scientific and political comprehension of the vaccine-related obstacles. Such efforts, adjustable to meet specific community needs, will set the stage for realistic expectations and understanding of the COVID-19 vaccine, updated vaccine versions, and related public health concerns, thus restoring trust in vaccine science more generally. This pathway can be utilized in other global locations and future pandemics.

State of COVID-19 Vaccination in the United States

Although vaccines have been effective in preventing diseases that we rarely observe today (e.g., pertussis and polio), historical and contemporary events reveal that there are reasons why Americans may mistrust vaccines or hold unrealistic expectations about them. For example, the COVID-19 vaccine, especially because it was developed at "warp speed," elicits safety, compliance, and distribution concerns among Americans. There are also several unknowns about the vaccine (e.g., length of vaccine protection and effectiveness against new SARS-CoV-2 variants) that both create friction with lay expectations and confront some individuals' mistrust in science. In particular, at least two COVID-19 vaccine versions, namely Pfizer/BioNTech and Moderna, use mRNA techniques which are a new biotechnical approach for which long-term effects are unknown.

If people do not complete the COVID-19 vaccine series, including the recommended booster; do not continue behavioral defenses (e.g., mask-wearing, social distancing); and fail to recognize that there are unidentified limitations to the vaccine's effectiveness, will they inhibit our ability to suppress transmission of the disease? If the vaccine fails to be a magic bullet for these reasons, will individuals blame the vaccine and then elevate general mistrust in vaccine science? To be effective, the COVID-19 vaccine may need to continue to be combined with behavioral protections (e.g., mask-wearing) in some U.S. settings, along with clear communication that scientific uncertainty should not breed mistrust, at least until and if herd immunity can be achieved. Reinforcing these concerns, COVID-19 has currently infected over forty-nine million people in the U.S. and resulted in over 780,000 U.S. deaths so far (Johns Hopkins University and Medicine, 2021; Our World in Data, 2021). To provide perspective, the number of COVID-19 deaths to date are equivalent to the populations of the U.S. cities of Denver, Colorado, or; Seattle, Washington, or; El Paso, Texas, or; Detroit, Michigan (World Population Review, 2021). Thus, why would a country that has lost the equivalent of the populations of entire cities from COVID-19 refuse a vaccine which has demonstrated it does not increase mortality among COVID-19 recipients, as well as has decreased serious morbidity and mortality from the disease? (Scobie et al., 2021; Xu et al., 2021). Vaccine hesitancy may play a significant role in these outcomes to date.

Vaccine Science Mistrust

The Centers for Disease Control and Prevention (CDC), the premier public health agency for the U.S. responsible for promoting health and preventing disease, has provided education to prevent the spread of COVID-19 at the personal, community, and school levels (Centers for Disease Control and Prevention, 2021a). Despite CDC identifying vaccinations as one of the greatest public health achievements of the 20th century because they increased longevity and improved population health status, vaccines and their administration have resulted in rare, but grievous, errors, thus generating public mistrust when adverse events occur (Centers for Disease Control and Prevention, 1999; Centers for Disease Control and Prevention, 2021b). Notorious examples include the 1955 Cutter Incident in which live polio virus in a vaccine batch (produced by Cutter Laboratories) that had undergone a safety review prior to administration resulted in approximately 250 cases of polio, although, later it led to an improved regulatory system for vaccine production (Centers for Disease Control and Prevention, 2021c). Another example involves Gardasil, a vaccine that prevents cervical cancer caused by the human papillomavirus. In 2013, a manufacturing error resulted in the potential for broken glass in the vaccine vial, leading to Gardasil's recall. No adverse health effects were reported (Centers for Disease Control and

Prevention, 2021c). These examples and other purported, and even sometimes discredited, vaccine-related adverse health effects [e.g., measles-mumps-rubella (MMR) vaccine and autism] have contributed to the public's mistrust of vaccine science and safety (Centers for Disease Control and Prevention, 2021c). Some individuals are hesitant about all vaccines for non-scientific reasons ranging from philosophical rationales to suspected conspiracies (Calandrillo, 2004). Hence, the development of a novel COVID-19 vaccine should expect to encounter widespread resistance in adoption if history is any indicator of future practice.

We see parallels from these historical examples and the current COVID-19 vaccine where conspiracy theorists and some influential voices promote false information, such as the claim that the U.S. Food and Drug Administration is not telling Americans that the COVID-19 mRNA vaccines cause serious side-effects including death (Fichera, 2021; Frenkel, 2021). There is historical precedent for this; for example, Walter Winchell, one of the most famous broadcasters in the U.S., broadly aired a misleading story about the Salk vaccine's safety during the preparations for the national trials in 1954 (Money, 2021). Currently, belief that the seriousness of the SARS-CoV-2 virus has been exaggerated to sway political elections has contributed to vaccine hesitancy among many conservative Americans (Uscinski et al., 2020). Beliefs that the COVID-19 vaccine causes infertility and that a micro-chip is injected into individuals who receive the vaccine contributes to vaccine hesitancy globally, such as in Arab countries, in addition to the U.S. (Berg, 2021; Black and Schoolov, 2021; Sallam et al., 2021). Further, the indeterminant origin of the SARS-CoV-2 virus (i.e., bioweapon or a naturally occurring event) has also contributed to mistrust among the U.S. population about the seriousness of COVID-19 (McNutt et al., 2021). These select examples, along with a reliance on social media as a main source for COVID-19 vaccine information (Lazer, 2021), demonstrate a significant obstacle to controlling the COVID-19 pandemic.

COVID-19 Vaccine Hesitancy Behavior

While beliefs in conspiracy theories, combined with mistrust in science, policymakers, and governmental information channels may contribute to COVID-19 vaccine (including booster) hesitancy (Simione et al., 2021), awareness of the underlying psychological basis for vaccine hesitancy and recognition of enhanced levels of hesitancy in certain demographics may improve our ability to respond to the current and future pandemics. Several studies have determined a positive correlation between vaccine hesitancy and the following psychological factors: belief in conspiracy theories; absence or low fear level of COVID-19 health effects; fear of potential side effects from a vaccine that many still consider too new; and philosophical or religious beliefs that are not consistent with seeking the COVID-19 vaccine (Nazlı et al., 2021). With regard to demographics, women have demonstrated a greater hesitancy than men towards the vaccine before its release (although more females have received the vaccine in the U.S.), and to date, Black and Hispanic populations have been more hesitant than their White counterparts to receive the first dose of the COVID-19 vaccine in the U.S. (Centers for Disease Control, 2021; Kaiser Family Foundation, 2021; Stanford University, 2021).

An international comparison demonstrates that philosophical approaches to vaccination and public health may have an impact on hesitancy, too. A comparator country to the U.S., in terms of societal development, is the United Kingdom (U.K.) which has experienced over ten million COVID-19 cases and 146,000 deaths to date (Johns Hopkins University and Medicine, 2021; Our World in Data, 2021). Yet, the U.K. approach to the COVID-19 vaccine has been more from a collective societal benefit attitude compared to the U.S., which is a more individualistic society (Feuerstein et al., 2021). This philosophy has resulted in an overall low vaccine hesitancy rate among the British population with higher vaccine hesitancy rates occurring in those who have a low education level, are female, in the 16–24 age group, and those of a Black or Pakistani/Bangledeshi ethnic group (Robertson et al., 2021). To an extent, the contrasting American perspective has had a different impact on some of the same demographic groups in the U.S.; for example, those in poverty, working outside of the home, or of a conservative political viewpoint were found to be more unwilling to acquire the COVID-19 vaccine (El-Mohandes et al., 2021).

Successful messaging also requires recognition that hesitancy may stem from immediate opportunity costs as well. For example, some individuals refused smallpox vaccinations at the turn of the 20th century because of concern that a resulting temporarily sore and incapacitated arm meant the recipient could not earn a living and feed his family; he might avoid smallpox later, but he and his loved ones might suffer now (Willrich, 2012a). Today, concerns about losing pay if one took time off work to get a COVID-19 vaccine because of side-effects have increased some reluctance, especially among demographic groups, such as Hispanics, who are often more vulnerable to economic instability (Hamel, 2021).

To resolve hesitancy generated by misinformation about the COVID-19 disease, vaccine, and boosters, as well as psychological, demographic, philosophical, economic, or other issues, requires building trust among the intended audience. One approach is for experts to contextualize the information they are communicating based on what is known at the time of the messaging and informing the audience that the information could change as more is learned about the disease, transmission, mitigation, and prevention efforts (Jamieson, 2021). Respect for the legacies of historical experiences may be necessary, too. Black distrust of the medical establishment, stemming from ill-treatment in the Tuskegee syphilis study, influences current wariness about vaccine recommendation (Koplowitz, 2021). In fact, some descendants of the men in the study are speaking out in favor of the vaccine, explicitly recognizing history's impact on current reluctance (O'Reilly, 2021). Also, it is possible that a traditional protein-based vaccine, like those made for influenza and shingles, but developed specifically for COVID-19, could help allay the fears of a vaccine hesitant population who are concerned about the potential mRNA COVID-19 vaccine side-effects (e.g., heart inflammation and blood clots). The protein-based COVID-19 vaccine is currently being tested in national efforts in Cuba and Taiwan (Dolgin, 2021a).

Historical and current events suggest that understanding the reasoning behind reluctance, transparency in how recommendations are developed, providing reputable sources of information, and then educating the population about the basics of public health, could help to promote an educated citizenry who is more apt to make informed, rational decisions based on evidence as opposed to conspiracies and fake news.

Novel COVID-19 Vaccine

Operation Warp Speed (OWS) aimed "to deliver 300 million doses of a safe, effective vaccine for COVID-19 by January 2021, as part of a broader strategy to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics" (U.S. Department of Health & Human Services, 2021). It is reasonable to believe that the public expected that any COVID-19 vaccine be effective and safe, and its distribution be equitable and transparent (National Academies of Science et al., 2021). Hence, a mass medical intervention for the COVID-19 vaccine must overcome several select challenges outlined below.

Safety

What is novel about reluctance to receive a COVID-19 vaccine are new concerns, namely that the rushed scientific process is flawed or will produce a vaccine that is not only ineffective but also dangerous. A survey implemented during the vaccine development and testing stage in 2020 reported that 50% of Americans may refuse a COVID-19 vaccine; of the 20% who planned to reject it, 70% cited safety concerns, such as the inability to see if health problems developed during clinical trials, as their motivation (Cornwall, 2020; Neergaard et al., 2021). As of early December 2021, approximately 469 million doses of the COVID-19 vaccine have been administered with 197 million Americans fully vaccinated (which may require a person to receive two doses and be 2 weeks past the second dose) representing only 59.8% of the U.S. population, despite the eligibility of everyone aged 5 and over (CDC, 2021; Mayo Clinic, 2021). While some statistics may reflect logistical challenges, including access to a vaccination site and scheduling conflicts, in some places available vaccines go unused (FEMA, 2021).

The reality that vaccines lead to iatrogenic harm has historical foundation, and even current, official recognition. The National Vaccine Injury Compensation Program acknowledges that government-approved vaccines cause serious harm to a few individuals, often because of allergic reactions. The Program protects vaccine manufacturers and healthcare providers from legal damages that would deter them from offering vaccines, thus weakening societal protection against diseases (Health Resources and Services Administration, 2021a). An addendum, inspired by the 2009 influenza pandemic, the Countermeasures Injury Compensation Program (CICP), focuses on pandemics and other emergency defenses that produce unintended injury, suggesting government awareness that rapidly developed and somewhat experimental treatments or protections might harm patients (Health Resources and Services Administration, 2021b). CICP's extended protection for COVID-19 vaccines treats them like other vaccines and experimental treatments, yet it acknowledges the dangers inherent in emergency measures (Health Resources and Services Administration, 2021c).

Furthermore, history demonstrates that there can be multiple rationales for questioning vaccine safety. For example, smallpox vaccines tainted with tetanus killed over 13 children in 1901, leading to popular resistance against the mandatory vaccine (Willrich, 2012b; Bencks, 2021). The Brodie-Park and Kolmer polio vaccines led to six deaths from polio, another six cases of it, and systemic infection, as well as widespread inflammation in other children—out of a testing pool of 19,000 children in 1935 (Kluger, 2021). The military mandates smallpox vaccines for some soldiers, despite noticeable side effects, particularly for those with heart ailments (Military Health System, 2021). In these cases, local or federal governments approved the vaccines while reputable pharmaceutical companies developed and manufactured them.

Regardless of these problems, vaccines have saved millions of lives. Still, current recognition that there can be dangers in approved vaccines means that the lay concerns about safety have a long and reasonable basis. Some experts, such as the Association of American Medical Colleges, warned about a COVID-19 vaccine produced too rapidly and incautiously. This stance recognizes that the rapid timeline for COVID-19 vaccine invention and availability is unsettling since vaccine development and the human body's response (e.g., antibody production and vaccine side effects) both can occur slowly (Boyle, 2021). In contrast, federal officials reassured the public that some challenges that slowed past vaccines' development have been overcome; these include identification of the genetic make-up of SARS-CoV-2 (a years-long process in polio), recent advances in vaccines for similar diseases (e.g., Middle East Respiratory Syndrome), and funding and contracts to anticipate manufacturing needs (e.g., syringes) (Padron-Regalado, 2020; Zhang, 2020; Pawlowski, 2021). Still, public concerns have some basis (e.g., the likely association between the COVID-19 vaccine and rare heart conditions in young people, discovered after vaccine administration began) (Centers for Disease Control and Prevention, 2021d), but the political pressure in the current situation exacerbates them, seemingly more than scientific advances calms them.

Administration

Common consensus is that safe vaccines offer absolute protection against viruses. After all, they have rid the world of smallpox and are close to eradicating polio. Perhaps that is one reason that the flu vaccine engenders grumbling: it is a well-known exception. It fails to safeguard against all influenzas; one needs a new vaccine annually; and it neither protects the recipient immediately nor completely (at times less than 40%) (Centers for Disease Control and Prevention, 2021e). Yet, expectations exist that vaccines should provide a perfect shield, or, at the very least, that there is a known pathway to full protection, such as a specific series of shots on a set schedule followed by a booster at particular intervals. The COVID-19 vaccination adheres to similar rules. With less than 60% of the U.S. population fully vaccinated, have uncertainties about key elements of successful vaccine

administration (e.g., compliance, compulsion, and effectiveness) shaped Americans' behavior and expectations about a COVID-19 vaccine? Will violated expectations hinder a vaccine's ability to help suppress the pandemic? If so, will one repercussion be an increased mistrust in vaccines?

Compliance and Compulsion

- Will individuals get both doses of a two-shot COVID-19 vaccine (e.g., Pfizer/BioNTech's option) and any booster? CDC reports approximately 70% compliance with a seven-disease early childhood vaccine schedule (National Center for Health Statistics, 2021). Is there any reason COVID-19 compliance will be higher, especially when some incomplete vaccination records arise from reasons unrelated to COVID-19, such as failure or inability to return to a vaccine administration location or provider? In the U.S., for example, the 7-day average for those partially vaccinated is currently 71.1% (Our World in Data, 2021). What are other reasons individuals do not become fully vaccinated when many communities have extended clinic hours, mobile clinics, and walk-in clinics at local pharmacies?
- Will it be possible to require the vaccine, thus increasing compliance? *Jacobson v. Massachusetts*, a 1905 U.S. Supreme Court case, governs the state's ability to require vaccines (Jacobson, 1905). Henning Jacobson could be jailed and fined—or today, we see children excluded from school—when he refused a smallpox vaccine, but the government could not immunize him forcibly. That still applies, but private employers have begun to bring pressure that different loci and agencies of government may not have applied (State Covid-19 Data and Policy Actions, 2021). Even before COVID-19, some hospitals made annual influenza immunization a condition of employment. In June 2021, the U.S. District Court ruled that Houston Methodist healthcare could require workers be vaccinated against COVID-19 after approximately 100 individuals sued, claiming the vaccine was "experimental and dangerous" (Jacob Gershman, 2021). Might other employers attempt similar tactics in the form of an "immunity passport," converting debate about mandatory vaccination into debate about individual rights versus public health, similar to the one we see about mask-wearing (Branswell, 2021a; World Health Organization, 2021)? While the U.S. Equal Employment Opportunity Commission allows employers to ask about COVID-19 vaccination status, it must keep that data private. Some companies, though, have plans to make information public by differentiating between vaccinated and unvaccinated workers with different rules about mask-wearing or lanyard identification colors (U.S. Equal Employment Opportunity Commission, 2021). Will COVID-19 vaccination status become public knowledge, and could this extend to other infectious diseases (e.g., hepatitis or meningitis)?
- Can the federal government compel vaccination in new ways? In the Fall 2021, President Biden announced that the COVID-19 vaccine is required for federal employees, businesses with more than 100 employees, healthcare workers, teachers, and school staff, to name a few sectors. President Biden also urged the acquisition of the COVID-19 booster following the initial dosing regimen (Kavi, 2021). Currently, this time-sensitive, federal mandate that was brought forth by the Occupational Safety and Health Administration (OSHA) is on hold in the 5th circuit due to legal challenges to OSHA's authority and the breadth of the requirement (Engelhardt, 2021; Krisher, 2021). It is likely that the legality of the COVID-19 vaccine mandate will be heard by the U.S. Supreme Court which is expected to rule in favor of the vaccine mandate based on a framework of legal and public health safety regulations (Breuninger, 20212021), including the precedent case of *Jacobson v. Massachusetts*.
- What are other venues for government compulsion of vaccination, ones that strive to reach wider groups or vulnerable ones? Governmental entities below the federal level have also begun to explore vaccination mandates, particularly for access to activities. One of the broadest is in New York City where vaccine requirements for restaurant dining, indoor physical activities, and entertaining options are expanding even as access to vaccines grows to include younger children (NYC Health, 2021). Some mandates focus on particular demographic groups; California has promulgated a vaccine requirement for students, likening the COVID-19 vaccine to other required vaccines against communicable diseases necessary for children who spend hours a day in proximity and thus may be particularly susceptible to easily transmissible illnesses (Office of Governor Gavin Newsom, 2021).

Effectiveness

- Will a COVID-19 vaccine thwart lay expectations because it requires time after administration before it shields an individual? The annual influenza vaccine necessitates approximately 2 weeks before it protects someone. However, if someone develops influenza before then, the common misperception is that the flu vaccine failed, or the vaccine transmitted the flu. The National Opinion Research Center at the University of Chicago reported that approximately 31% of respondents feared becoming ill from the influenza vaccine, and the same number thought it was ineffective (NORC at the University of Chicago, 2021). How many people get COVID-19 before their immunization is fully effective? One study suggested that subjects were 80% protected 2 weeks after the first vaccine dose of Pfizer/BioNTech or Moderna, but approximately 90% protected 2 weeks after the second vaccine dose (Branswell, 2021b). Will individuals attribute sickness before full protection to an ineffective vaccine, as many do with regard to the flu?
- Currently, we are observing how long the COVID-19 vaccine's protection lasts and whether it will provide protection against all disease variants, such as Omicron (Yong et al., 2019; Callaway and Ledford, 2021). In the

1990s, researchers recommended adults receive pertussis boosters because statistics revealed increasing numbers of whooping cough cases in vaccinated adults (Cherry, 1996). At the end of 2021, experts engaged in vigorous discussions about the need for, and value of, boosters before the CDC recommended boosters for all adults (Dolgin, 2021b). Recipients of a COVID-19 vaccine are in a large natural experiment testing the robustness of the vaccine.

- Vaccines must be safe and effective, but they need not be 100% effective. In 1955, Dr. Tommy Francis announced the results of a national polio vaccine trial involving nearly two million children. Jonas Salk's vaccine prevented 68–100% of different polio strains, thus serving as a new weapon against polio (Kluger, 2004). Between immunizations, herd immunity, and personal protective practices (e.g., covering mouth when coughing), many formerly catastrophic diseases essentially have been eliminated in the U.S. We have witnessed people relax or renounce mask-wearing and other protective actions because they expect a COVID-19 vaccine will immediately protect them from sickness, not just serious illness or death. Yet, in some settings, despite vaccination against COVID-19, mask-wearing may be warranted, perhaps to enter a retail business (Money, 2021). Will such recommendations result in decreased visitation to such venues? In contrast, polling suggests that at least 25% of unvaccinated individuals may not wear a mask, even when that is optional only for those vaccinated (Motta, 2021). How will personal protective practices be influenced as we witness that the COVID-19 vaccine can be an effective mitigator that lessens the severity of a case but may not prevent the disease altogether?

Distribution

Traditionally, the federal government allocates doses to states, while the latter establishes distribution guidelines (including who has priority and who may be inoculated) and even punishments if they are violated. In 2009, during the H1N1 flu vaccine shortage, some states gave the most vulnerable individuals preference while Maine named healthy children as potential vectors and thus as priority vaccine recipients (Ruiz, 2009; Bristow et al., 20172021). State-based discretion led to varied policies, especially since states had different stockpiles, needs, and interests. Individual states allocated COVID-19 vaccine based on their respective populations and federal guidance. The National Academy of Medicine created guidelines, and OWS proclaimed control over this, although normally the National Advisory Committee on Immunization Practices provides recommendations to the states (Branswell, 2021c). Individuals already debating the state governments' rights to mandate masks in public or establish stay-at-home orders for COVID-19, may also perceive government-determined distribution and, perhaps, employer or government compulsory orders for immunization, as threats to individual liberties, even if that weakens public health. The fact that new agencies developed the national COVID-19 vaccine guidelines, and that certain groups received priority for immunization and boosters, may challenge public expectations and increase frustration, if not misunderstanding and mistrust of scientific priorities.

DISCUSSION

We look to public health to offer the following recommendations as we prepare for the continued management of an effective and safe COVID-19 vaccine and necessary COVID-19 vaccine booster:

1. Encourage scientists, politicians, and the public to clear confusion and increase respect for each other by:
   - Recognizing that mistrust of vaccines comes from a range of current and historical experiences; anti-vaccination stances cannot simply be dismissed as being ignorant.
   - Implementing two-way communication between the public health experts and the lay public so views and misunderstandings about COVID-19 and other public health issues can be discussed and addressed. Communicate in a transparent manner that emphasizes the state of knowledge at the time of the messaging. Also, evolution of messaging is expected as new information is learned about public health issues of concern.
   - Engaging in discussions to help the public, government, and communities establish realistic expectations about what a COVID-19 vaccine can achieve and how it will be distributed. How can communities best control COVID-19's spread while balancing personal freedom with the protection of the population's health?
2. Adopt actions to increase the likelihood of COVID-19 vaccine and booster adoption:
   - Consider providing vaccine education and vaccination clinics in places where the community spends its time (e.g., work and school), thus lowering logistical barriers to vaccination (Cornwall, 2020).
   - Develop and implement community vaccine policies, with the assistance of the public, that are fair and transparent.
3. Encourage public health education in the general population to ensure a citizenry competent in the basics of public health functions. One that is:
   - Prepared to understand and act upon ongoing and novel public health problems.
   - Able to recognize that what appears as conflicting messaging in the media can be rather understood as the scientific process in action.
   - Assure trusted voices in the community (e.g., physicians, clergy) are heard.

These recommendations could be viewed through the lens of risk communication which requires effectively communicating science and health risk (Environmental Protection Agency, 2021). The governmental officials responsible for monitoring community and national health threats should be skilled in a way that they can clearly and effectively present the immediate and long-term risks of the issues at hand, the magnitude of the threat, and steps to mitigate and/or prevent adverse health outcomes. Concomitantly, the public needs to be educated to understand the significance, prevalence, and incidence of a disease threat, the difference between morbidity and mortality, and the health purpose for recommended actions that may limit

one's personal freedom to a small (e.g., mask-wearing) or large degree (e.g., COVID-19 vaccine mandate) in juxtaposition to the physical, mental, emotional, and economic health of society. The COVID-19 vaccine response should be tailored to meet populations' needs. Stakeholders are likely to accept vaccine distribution policies, despite their level of controversy, if they are evidence-based, realistic, equitable, transparent, and include the input and concerns of those affected.

While COVID-19 is a new health threat, and the vaccine was developed at an unprecedented rate, the core challenges presented with respect to vaccine safety, administration, and distribution are timeless, although accompanied by unique circumstances that increase their complexity. We present considerations about the safety, administration, and distribution of the COVID-19 vaccine and offer recommendations for responses to this ongoing, unique public health event. The steps scientists, governments, and communities take to enhance U.S. vaccine deployment and reduce vaccine hesitancy may save lives threatened by COVID-19 today and in the future. These steps also may apply, and even improve, the protection of global populations facing COVID-19 and its variants, as well as other emerging infectious diseases.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

RC proposed the topic for discussion. RC and MD co-developed the manuscript outline and co-wrote the article. All authors contributed to the article and approved the submitted version.

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Correlation Between Previous Caesarean Section and Adverse Maternal Outcomes Accordingly With Robson Classification: Systematic Review and Meta-Analysis

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Background: The increasing rates of Caesarean section (CS) beyond the WHO standards (10–15%) pose a significant global health concern.

Objective: Systematic review and meta-analysis to identify an association between CS history and maternal adverse outcomes for the subsequent pregnancy and delivery among women classified in Robson classification (RC).

Search Strategy: PubMed/Medline, EbscoHost, ProQuest, Embase, Web of Science, BIOSIS, MEDLINE, and Russian Science Citation Index databases were searched from 2008 to 2018.

Selection Criteria: Based on Robson classification, studies reporting one or more of the 14 adverse maternal outcomes were considered eligible for this review.

Data Collection: Study design data, interventions used, CS history, and adverse maternal outcomes were extracted.

Main Results: From 4,084 studies, 28 (n = 1,524,695 women) met the inclusion criteria. RC group 5 showed the highest proportion among deliveries followed by RC10, RC7, and RC8 (67.71, 32.27, 0.02, and 0.001%). Among adverse maternal outcomes,

hysterectomy had the highest association after preterm delivery OR = 3.39 (95% CI 1.56–7.36), followed by Severe Maternal Outcomes OR = 2.95 (95% CI 1.00–8.67). We identified over one and a half million pregnant women, of whom the majority were found to belong to RC group 5.

Conclusions: Previous CS was observed to be associated with adverse maternal outcomes for the subsequent pregnancies. CS rates need to be monitored given the prospective risks which may occur for maternal and child health in subsequent births.

Keywords: previous caesarean section, adverse maternal outcomes, World Health Organisation - Robson Classification, women's health, public health practice, global health

INTRODUCTION

High rates of maternal mortality due to the common preventable causes like haemorrhage, eclampsia, and sepsis (1) call for safe procedures like Caesarean Section (CS). Although, theoretically, the procedure is intended to protect against the adverse maternal outcome, the increase in caesarean rates in low and middle-income countries has not been associated with improved perinatal outcomes (2). In addition to increased risk of neonatal and perinatal mortality in vaginal birth after caesarean (VBAC) (3), previous CS has been reported as being associated with adverse outcomes of subsequent pregnancies such as maternal mortality, blood transfusion, admission in critical care, and hysterectomy (4–6).

In 2014, the WHO proposed Robson classification for assessing, monitoring, and comparing caesarean section rates within and between healthcare facilities over time (7). The system classifies women into 10 mutually exclusive groups. There has been no previous study with a systematic review design followed by a meta-analysis that specifically discusses the history of caesarean section (repeated) with maternal and perinatal adverse outcomes by grouping the women based on the WHO classification. Previous studies have reported a relationship between the history of caesarean section and individual adverse maternal outcomes rather than pooled evidence on several maternal outcomes. The current review and meta-analysis aim at assessing women according to Robson's classification and to report pooled evidence on the impacts of previous CS on outcomes of the subsequent pregnancy.

METHODS

Search Strategy and Selection Criteria

In this systematic review and meta-analysis, the literature was extracted by systematic search from two electronic platforms, Ovid system and Web of Science, which provided access to eight databases, including PubMed/Medline, EbscoHost, ProQuest, Embase, Web of Science, BIOSIS, MEDLINE, and Russian Science Citation Index. Studies that met all of the following criteria were regarded eligible to be included in this review: original papers reporting findings from relevant randomised controlled trials or observational study designs (cohort, cross-sectional and case-control studies) following strengthening the Reporting of Observational studies in Epidemiology (STROBE) criteria) (8), published in the English language between 2008 and 2018. Studies reporting previous CS for all participants, adverse maternal events as the outcome variable, and those providing sufficient statistical data (risk estimates) were included in this research. Only those researches were included, which were conducted on participants who had had at least one prior CS and could be classified as Robson 5,7,8,9, or 10 according to Robson classification described by the WHO (9). Studies reporting one or more of the following 14 adverse maternal outcomes were considered eligible for this review: analgesia/anaesthesia, blood transfusion, heavy bleeding, hypertension, hysterectomy, infection, maternal death, pre-eclampsia, placenta previa, preterm delivery, retained placenta, severe maternal outcomes (SMO), uterine dehiscence, and uterine rupture. The studies were excluded if they failed to report the predefined independent (CS) and outcome variables (adverse maternal outcomes), provide sufficient statistical information, were case reports, opinions, or comments on other research, were published before 2008 or after 2018, or were published in languages other than English.

The search strategy, inclusion and exclusion criteria, and extraction methods were agreed upon by all authors. Literature search and data extraction were done by one author (RN) and reviewed by another (UI). To increase sensitivity to potentially appropriate studies, free-text terms with initial keywords "caesarean section history," "adverse maternal outcomes," and Medical Subject Headings (MeSH) were used (**Supplemenatary Table 1**). In addition to the agreed-upon search strategy, citations from eligible articles were also sought for relevant literature. After title and abstract review and screening for duplicates, full texts of potentially relevant articles were examined by two independent reviewers. Variables that were extracted from each article were publication year, study setting, investigation time, study design, method of assessing the outcomes, current delivery process, indication, and current maternal outcome.

Quality Assessment

The risk of bias (ROB) of randomised control trials was assessed with Cochrane ROB tools ver.2.0 (10). For observational designs (cohort, cross-sectional, and case-control), STROBE criteria (8) and The Newcastle-Ottawa Scale (NOS) by two independent reviewers were used for quality assessment. In assessment with NOS, a star rating system was adopted with the following

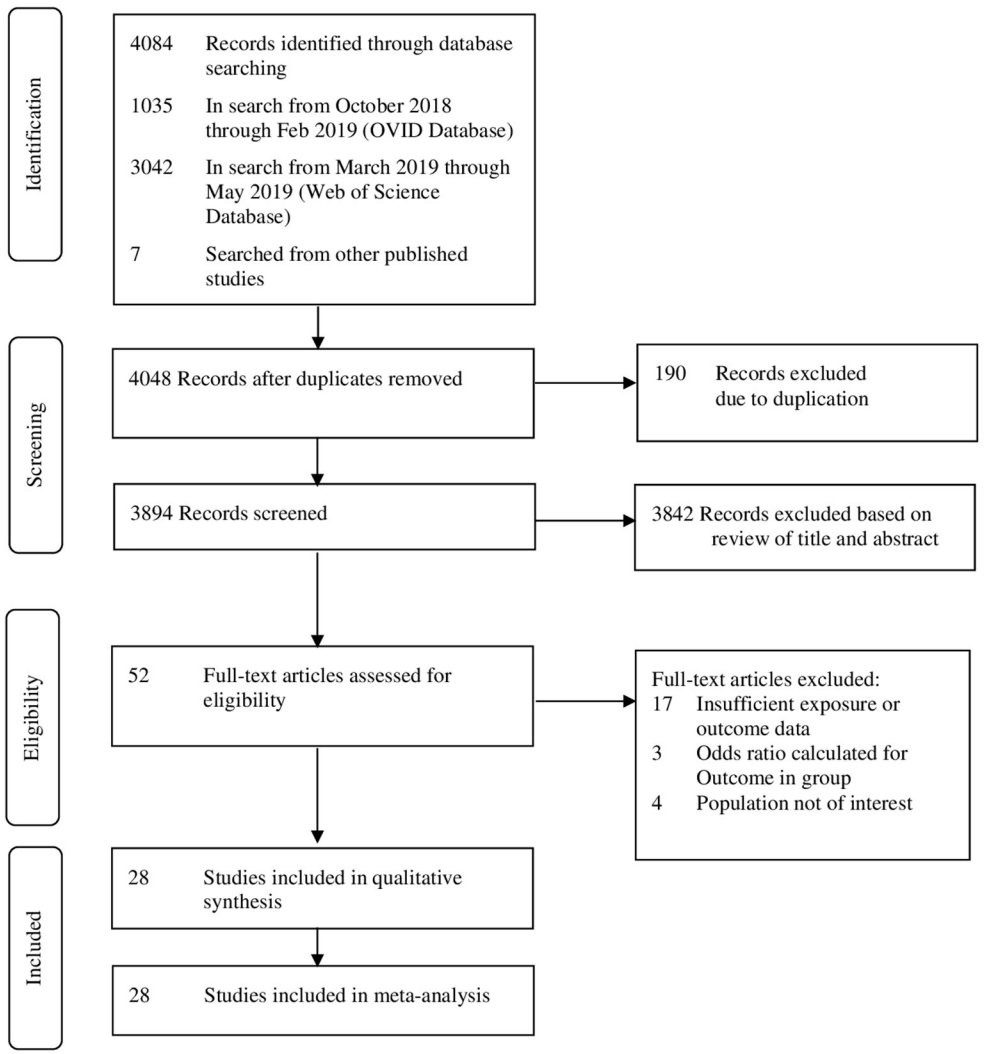

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses (PRISMA) framework for study selection.

classification: 0–4 stars defined as low-quality, 5–6 stars defined as medium quality, and 7–9 stars as high-quality.

Data Analysis

The eligible studies were subjected to qualitative synthesis and statistical analysis. Epidemiological measures of risk reported in the studies, including Odds Ratio (OR), Hazard Ratio (HR), and Relative Risk (RR), were used to calculate binary outcomes and were reported as OR with 95% Confidence Interval (CI). Data on ORs extracted from studies after being grouped by adverse maternal outcomes was pooled using the random-effects model. The extracted pooled ORs for individual outcomes were combined to construct summary pooled ORs. $\tau 2$ values arising from the random-effects models were used to quantify heterogeneity among individual studies. Although the primary analysis involved all eligible studies, a secondary subgroup analysis of studies stratified based on RC was also conducted. A pooled proportion for maternal outcomes was determined for each of the RC categories using the random effects model. The statistical analysis was done using comprehensive meta-analysis and checked for accuracy. The developed protocol was prospectively registered in PROSPERO (registration number CRD42018103943).

RESULTS

Study Characteristics

From the initial 4,084 records, 52 articles qualified for full-text review, of which 28 were included in systematic review and meta-analysis (**Figure 1**). Overall, 11 prospective studies, 14 retrospective studies, one RCT, one cross-sectional, and one case-control study were included. The studies were published between 2008 and 2018 with retrospective cohorts starting from 1975. Studies reported data from six different continents. Four studies

were from America (three from US and one from Canada), five studies from Australia, nine studies from Europe, seven studies from Asia, and three studies from Africa. There was also one study that covered 29 countries in Africa, Asia, Latin America, and the Middle East. Sample sizes ranged from 22 to 6,85,137 women, involving 1,524,695 women who underwent CS in the previous pregnancy (**Table 1**).

Link Between Previous Caesarean Section and Adverse Maternal Outcomes

The most common adverse maternal outcomes reported were heavy bleeding (reported in 15 studies) and uterine rupture (reported in 12 studies). Analgesia/Anaesthesia administration (98.21% in CS group, 93.84% in VBAC group), Infection (16.28% in CS group, 8.50% in VBAC group), and heavy bleeding (5.68% in CS group, 3,84% in VBAC group) were among the highest reported events (**Supplementary Table 2**).

The pooled evidence for risk of adverse maternal outcomes with previous CS has been shown in **Figure 2**. Random-effects analysis showed an association between previous CS with adverse maternal outcomes with an overall pooled effect size of 1.66 (95% CI 1.06–2.62) and heterogeneity as $\tau 2 = 1.48$. Of the adverse maternal outcomes, hysterectomy was found to have the highest association with previous CS after preterm delivery with OR = 3.39 (95% CI 1.56–7.36), followed by severe maternal outcomes with OR = 2.95 (95% CI 1.00–8.67).

Link Between Previous Caesarean Section and Adverse Maternal Outcomes Based on Robson Classification

The studies which qualified for the final analysis reported women belonging to four groups of Robson Classification (RC5, RC7, RC8, and RC10). RC5 was the most commonly reported group in the selected studies. The outcomes reported in RC5 varied into 13 different maternal adverse outcomes. Despite being the most commonly reported class, the overall pooled effect of RC5 with adverse maternal outcomes was found to be 1.32 (95% CI 1.01–1.74) (**Figure 3**).

Publication Bias

Among the four subgroups of Robson Classification, only RC5, as reported in 70 different studies, was regarded as eligible for assessment of publication bias. Assessment for publication bias was not performed for other groups ($\leq$5 studies). The funnel plot and Egger's test (**Figure 4**) showed no evidence of a significant small-study effect in the analyses between previous CS and adverse maternal outcomes for subgroup RC5 ($p = 0.20$).

Meta-Regression for Exploring Between-Study Heterogeneity

To explore the sources of study heterogeneity, meta-regression with covariates publication year, countries, study design, and the sample size was carried out. As individual-level data were unavailable, we used aggregate data for this purpose. The result showed there is no between-study heterogeneity ($p = 0.57$).

Quality Appraisal and Risk of Bias Assessment

Of the 27 observational studies assessed by the star rating system of NOS, one was regarded to be of low quality, 16 as medium quality, and 10 as high quality. One randomised control trial assessed by using Cochrane ROB tools (version 2.0) showed a low risk of bias (**Supplementary Figure 1).**

DISCUSSION

In this meta-analysis of the data of 1,524,695 individuals from diversified regions around the world, the previous CS was found to be associated with adverse maternal outcomes in subsequent pregnancy and childbirth. A two-way link between a history of CS and adverse maternal outcomes was observed. The odds of experiencing adverse outcomes for women who experienced repeat-CS was 1.61-fold the odds of someone who went through the VBAC.

Among the adverse outcomes studied, hysterectomy was one of the most common events. The odds of hysterectomy for women who experienced repeat-CS were found to be 3.390-fold the odds of someone who went through VBAC. This result is in accordance with a previous study that showed elective repeated caesarean delivery might be associated with a higher risk of hysterectomy and neonatal respiratory problems (38). Hysterectomy as a life-saving intervention is frequently needed for patients with previous CS, especially when the excessive blood loss treatment intervention has been done. Since the women in the repeat CS group had a higher rate of hysterectomy, this strengthens the association of previous CS with the adverse maternal outcomes that occur during the subsequent birth. Cephalic presentation in the Robson Classification group 5 is not the leading cause, but the previous CS has a significant association with the hysterectomy event. The underlying factors associated with the increased likelihood of hysterectomy are adherent placenta, placenta previa (39–41), postpartum haemorrhage (40), and previous CS (41, 42).

The odds of severe maternal outcomes for women who experienced repeat-CS were 3-fold the odds of someone who went through VBAC. There are two previous studies that have suggested that maternal near-miss (MNM) events and maternal deaths should be coupled to reflect SMO, providing a more robust variable for study. Previous caesarean delivery in relation to MNM and SMO has been explored and found that individuals with previous caesarean deliveries have an increased risk of MNM and SMO (43, 44). In this study, we excluded maternal death from the SMO group after introducing a separate maternal death outcome category. Interestingly, SMO was only reported by five different studies in Robson classification group 5. Women who experienced at least one previous CS with the cephalic presentation were more likely to have severe maternal outcomes in the subsequent pregnancy and childbirth. An enhanced probability of SMO/MNM has been reported to be associated with previous CS, high parity, and age (43).

TABLE 1 | Characteristics of studies included to find the correlation between previous caesarean section and adverse maternal outcomes.

References	Design	Place	Period	Women	Data Source/Setting	Objective
Asicioglu et al. (11)	Retrospective	Turkey	January 2005 and December 2010	364	Department of Maternal-Fetal Medicine of the Bakirkoy Women and Children's Teaching Hospital (Hospital A) and Şişli Etfal Teaching Hospital (Hospital B).	To investigate patient characteristics and foetal and maternal outcomes of placenta praevia and accreta
Baron et al. (12)	Retrospective	Israel	January 1, 1998, and December 31, 2011	5,635	Soroka UniversityMedical Center, Beer-Sheva, Israel	To investigate the maternal and perinatal outcomes in pregnancies associated with previous caesarean delivery and uterine scar dehiscence
Cogan et al. (13)	Retrospective	Belgium	August 2006 and March 2009	798	CHU Saint-Pierre University Hospital	To analyse, in a population of women who have a uterine scar, the maternal, foetal, and neonatal complications in relation to the mode of labour and delivery
Hammond et al. (14)	Retrospective	Australia	1984–2006	526125	Midwives Notification System (MNS) recorded in WA	To characterise changing risk factors of preterm birth in Western Australia between 1984 and 2006
Hu et al. (15)	Retrospective	China	January 2013 to December 2016	11662	International Peace Maternity and Child Health Hospital Data	To compare the perinatal outcomes of a subsequent pregnancy in women who underwent spontaneous vaginal delivery (SVD) or CS in their first delivery
Jastrow et al. (16)	Retrospective	United States	1989 and 2002	1,655	Ste-Justine Hospital Data	To evaluate obstetric outcomes in women undergoing a trial of labour (TOL) after a previous caesarean for dystocia in the second stage of labour.
Kessous et al. (17)	Retrospective	Israel	1993 and 2010	319	Soroka University Medical Center	To investigate whether vacuum extraction due to failure of labour to progress (dystocia) during the second stage in delivery following a previous caesarean section (CS) is related to increased adverse maternal and perinatal outcomes as compared with repeated CS.
Kugler et al. (18)	Retrospective	Israel	January 1988 and May 2006	1,102	Department of Obstetrics and Gynecology at the Soroka Database University Medical Center	To assess the risks of maternal and neonatal complications associated with VBAC compared to that of repeated elective caesarean section (CS) in the GMP population
Mone et al. (19)	Retrospective	Ireland	April 2010–April 2012	893	Northern Ireland Maternity System database.	To compare the characteristics of women who select elective repeat caesarean rather than a trial of labour after caesarean (TOLAC) for delivery, and to determine individual predictors for success and failure within a TOLAC group and observe differences in maternal and neonatal morbidity.
Motomura et al. (20)	Retrospective	29 countries in Africa, Asia, Latin America, and the Middle East	2010–2011	37,366	WHO Multicountry Survey on Maternal and Newborn Health (WHOMCS)	To describe the incidence, risk factors, and maternal and perinatal outcomes of uterine rupture among women with prior CS
Son et al. (21)	Retrospective	Illinois, United States	1999–2002	1,230	Caesarean Registry of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.	To compare maternal and neonatal outcomes that are associated with attempted operative vaginal delivery with those that are associated with second-stage repeat caesarean delivery without an operative vaginal delivery attempt among women who undergo a trial of labour after caesarean delivery
Stattmiller et al. (22)	Retrospective		2003–2011	685 137	Healthcare Cost and Utilization Project–Nationwide Inpatient	To evaluate the risk of adverse maternal outcomes associated with the trial of labour (TOL) after caesarean during subsequent pregnancies in the low-risk population.

(Continued)

TABLE 1 | Continued

References	Design	Place	Period	Women	Data Source/Setting	Objective
Tsai and Wu (23)	Retrospective	Taiwan	January 2006 and December 2015	400	Tamshui Branch of MacKay Memorial Hospital	To reveal the world trend in VBAC and our experience of a 10-year period in a medical centre in northern Taiwan
Yao et al. (24)	Retrospective	United States	2011–2014	5,38,264	National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention.	To estimate the maternal and neonatal risks associated with pregnancies that underwent TOLAC compared to those that elected for repeat caesarean delivery (RCD) in the obese population
Kabore et al. (25)	Prospective	Senegal and Mali	September 2007–October 2011	9,712	46 referral hospitals data	To assess the risks of uterine rupture, maternal and perinatal outcomes associated with a trial of labour (TOL) after one previous caesarean were compared with having an elective repeated caesarean section (ERCS) without labour in low-resource settings.
Kalisa et al. (26)	Prospective	Rwanda	June 2013 and December 2014	435	Ruhengeri district hospital medical records	To compare maternal and perinatal outcomes between ToL and elective repeat caesarean section (ERCS) at a district hospital
Al-Zirqi et al. (27)	Prospective	Norway	1 January 1999 to 30 June 2005	18,794	Medical Birth Registry of Norway (MBRN)	To determine the risk factors, percentage, and maternal and perinatal complications of uterine rupture after previous caesarean section.
Bakhshi et al. (28)	Prospective	United States	1999–2002	7,936	records from 19 academic centres	To describe the frequency of adverse maternal and neonatal outcomes at the time of repeat CD in women with a prior classical CD and compare these rates with those who had a prior low transverse CD
Belachew et al. (29)	Prospective	Sweden	1994–2006	2,58,608	Swedish Medical Birth Register	To evaluate whether women with a caesarean section at their first delivery have an increased risk of retained placenta at their second delivery
Crowther et al. (30)	Prospective	Australia	November 2002–May 2007	2,332	14 Australian Hospitals	To compare benefits and risks of a planned ERC with planned VBAC
Gilbert et al. (31)	Prospective	United States	1999–2002	22,068	The Caesarean Registry) by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network	To determine outcomes, after the use of propensity score techniques, to create balanced groups according to whether a woman undergoes elective repeat caesarean delivery (ERCD) or trial of labour (TOL)
Kalok et al. (32)	Prospective	Malaysia	February 2012–September 2012	186	tertiary teaching hospital	To determine the predictive factors for a successful vaginal birth after caesarean section (VBAC) and to develop a relevant antenatal scoring system
Kok et al. (33)	Prospective	Netherland	January 2000–December 2007	19,564	Netherlands Perinatal Registry (PRN) database	To determine neonatal and short-term maternal outcomes according to the intentional mode of delivery following a caesarean delivery (CD).
Schemann et al. (34)	Prospective	New South Wales	2007–2011	61,894	NSW population databases, the Perinatal Data Collection (PDC), and the Admitted Patient Data Collection (APDC)	To determine if case mix and hospital factors explain variation in hospital rates of repeat caesarean sections and whether these rates are associated with maternal and neonatal morbidity.
Studsgaard et al. (35)	Prospective	Denmark	March 2003–December 2010	1,783	Danish university hospital	To compare outcomes with the trial of labour after caesarean (TOLAC) or elective repeat caesarean delivery on maternal request (ERCD-MR)
Crowther et al. (30)	RCT	Australia	November 2002–May 2007	22	14 Australian Hospitals	To compare benefits and risks of a planned ERC with planned VBAC

(Continued)

TABLE 1 | Continued

References	Design	Place	Period	Women	Data Source/Setting	Objective
Litorp et al. (36)	Cross-sectional	Tanzania	February–June 2012	2,478	Uhimbili National Hospital in Dar es Salaam	To investigate if multiparous individuals who had undergone a previous caesarean delivery experienced an increased risk of severe maternal outcomes or adverse perinatal outcomes compared with multiparous individuals who had undergone previous vaginal deliveries
Homer et al. (37)	Case-control study	United Kingdom	February 2005 and February 2006	923	UK Obstetric Surveillance System	To examine whether the TGCS could be extended in a novel way to classify who required a peripartum hysterectomy

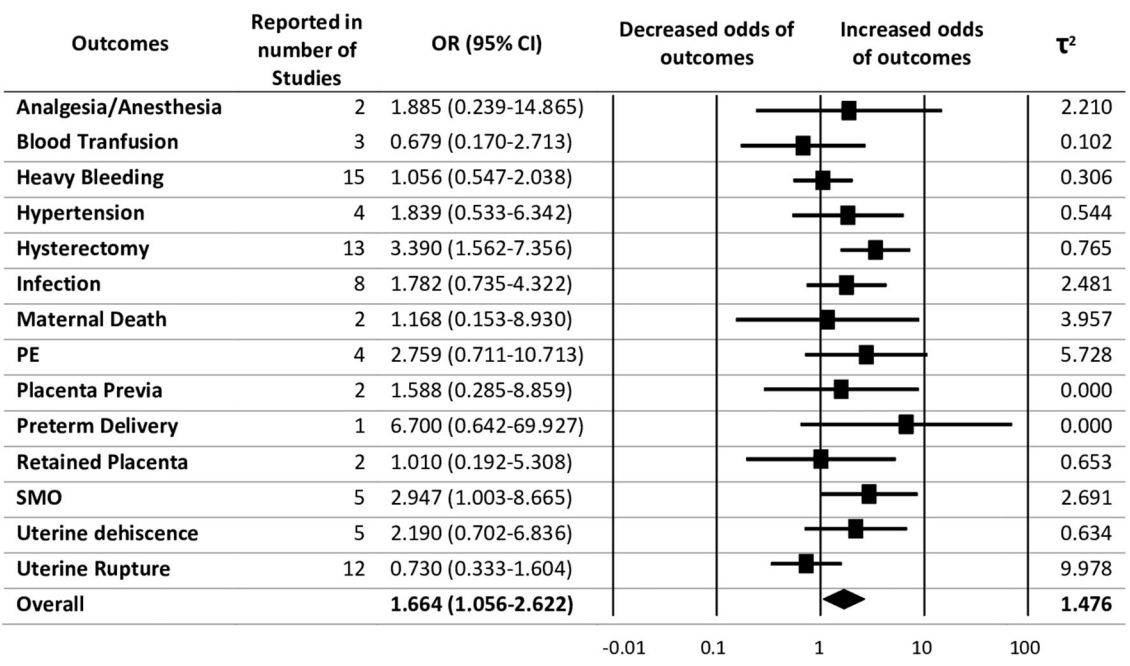

FIGURE 2 | Summary of pooled odds ratios (ORs) for the correlation between previous caesarean section (CS) with maternal adverse outcomes.

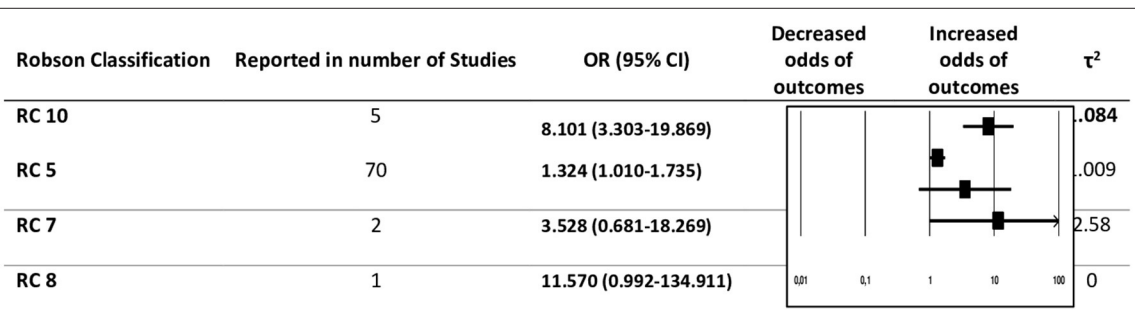

FIGURE 3 | Robson subgroup analysis with summary of pooled odds ratios (ORs).

We found that women who showed Pre-eclampsia outcomes were three times more likely to experience repeat-CS than those VBAC. Pre-eclampsia might be related to gravidity. Women giving birth to their fourth child through CS can be three times more likely to experience pre-eclampsia compared to gravida 1 (45). This study also revealed that women who have uterine

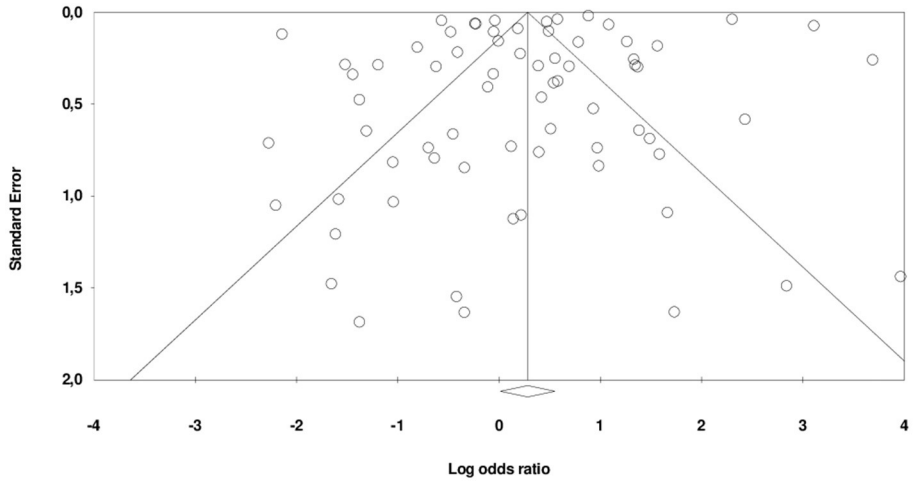

FIGURE 4 | Funnel plot RC 5 with adverse maternal outcomes.

dehiscence as the outcome are more likely to experience repeat-CS than those who had VBAC. Uterine dehiscence is a disruption of the uterine muscle with intact serosa (28). Uterine dehiscence and admission to the intensive care unit were more common in women with a prior classical CS. As a result of CS operation, late scar dehiscence may occur, which may lead to uterine rupture in a subsequent pregnancy (46). The uterine scar from previous CS is prone to be damaged due to both enlarged uterine and uterine contraction. The odds of hypertension for women who experienced repeat-CS were two-fold than those who went through VBAC. From three studies reporting hypertension as the adverse outcomes in RC group 5, one study has a diverse effect size. The effect size of this outcome reported in RC 10, the odds of women who has previous CS with premature birth are five-fold the odds of a woman who went through VBAC (OR = 5.16; 95% CI 4.52–5.89). Women with chronic hypertension are more likely to have various issues, including superimposed Pre-eclampsia and CS (47). It is also probable that other threat variables for chronic hypertension, including obesity and metabolism, will increase (48). Therefore, the number of women having a pregnancy with established chronic hypertension can result in an increasing rate of CS.

The current analysis showed that repeated CS was associated with a higher risk (about two-fold) of analgesia/anaesthesia administration than those who had VBAC. These findings are consistent with the previous study reported that those mothers who were treated with epidural analgesia during labour have higher chances of undergoing CS because of foetal distress (49). With the worldwide rise in the frequency of CS, the incidence of infection is anticipated to rise in conjunction, hence its clinical significance. Women undergoing repeat CS were twice likely to become infected than those undergoing VBAC. This finding is supported by a previous study that reported prior CS as one of the infection risk factors apart from maternal age, obesity, rural (as opposed to urban) dwelling, pre-gestational disease Mellitus, and pre-operative maternal condition (50). Post-CS infection usually results from a bacterial infection on the surgical site of the incision. Women with vaginal deliveries are less likely to get this infection. This study showed that infection cases were reported by eight different studies, even in women belonging to Robson Classification group 5. There was, however, no report regarding infection of women with previous CS with multiple pregnancies, oblique lie, breech presentation, or preterm pregnancy in the subsequent pregnancy and birth. There is evidence available to suggest the long term-effect of CS. With the rate of previous CS rising from 12 to 38% in over a decade, the placenta praevia frequency has increased. The occurrence of placenta praevia as the consequence where the lower uterine segment is scarred due to previous CS was reported by several studies (51, 52). In the current study, the odds of placenta praevia for women who experienced repeat-CS are almost two-fold the odds of a woman who went through VBAC. This outcome is associated with abnormalities in the endometrium triggered by prior scarring due to previous CS. In addition, in pregnancies with placenta previa and accreta, maternal age gives a significant contribution. Also, higher maternal age impairs ordinary placental growth as intramyometrial and endometrial arteries degrade with advanced maternal age (11).

In contrast to all other maternal outcomes, previous CS was found to be protective for blood transfusion and uterine rupture. Following a prior primary caesarean, a higher risk of blood transfusion has been reported to be associated with attempting VBAC compared with repeated CS (53). However, evidence also suggests opposing findings, suggesting the risk of blood transfusion is high in CS. Preoperative anaemia, high parity, and serious blood loss during operation lead considerably to the need for blood transfusion in patients experiencing CS (54, 55). These unexpected findings are probably because of

underreporting in the databases of each study leading to an underestimation of the effect.

We also found that women who have repeated CS were about 27% less likely to have uterine rupture as compared to those who had VBAC. According to the American College of Obstetricians and Gynecologists (ACOG), in a previous caesarean with a low transverse incision, the risk of uterine rupture in a vaginal delivery is about 1 chance in 500. Smith et al. published that women with failed VBAC are at higher risk of uterine rupture and perinatal death (56). Another study by Hochler et al. concluded a 0.3% risk of uterine rupture, and two cases ended in hysterectomy during their retrospective study to evaluate the safety of trial of labour after caesarean delivery in multiparous women (57). In this analysis, all of 12 studies reporting uterine rupture were in the RC group 5. This could contribute to some women being misclassified in the 10 groups because some of the studies excluded women with several comorbidities such as twin gestation and oblique lie.

There were no distinctions in the results between the repeated CS and the VBAC for preterm delivery, heavy bleeding (OR = 1.06; 95% CI.55–2.04), retained placenta (OR = 1.01; 95% CI.19–5.31), and maternal death (OR = 1.17; 95% CI.15–8.93). We could not report that preterm delivery has a very high association with the previous CS because, among the studies included in this review, there was only one study reporting preterm delivery as the outcome of the current birth after previous CS. Risk factors related to prior and existing obstetric problems (earlier premature birth, prior caesarean delivery, pre-eclampsia, and antepartum haemorrhage) were the most important predictors of premature birth and negative labour onset (14).

Even though this study resulted in no association between previous CS with heavy bleeding, retained placenta, and maternal death, the thorough clinical analysis identified retained placenta and co-occurring placenta praevia as the most common cause of haemorrhage (39). These factors were especially important for those women whose CS earlier. In keeping with guidelines by the Royal College of Obstetricians and Gynaecologists, the vast majority of women with previous CS had an antenatal ultrasound for placental location. Almost all women with retained placenta-indicated haemorrhage had previously delivered by CS (58). While it is recognised that the final diagnosis of the retained placenta can only be made during surgery, the occurrence of unreported instances shows the need for changes in antenatal identification.

The risk factors of the maternal death reported by two studies were postpartum haemorrhage, uterine rupture, pre-eclampsia/eclampsia, postpartum infection, and other obstetric complications (20, 25). Maternal death should be prevented by operative procedures, such as CS, given the changing birth patterns with higher CS rates in most countries. However, the increase in caesarean rates was not associated with improved outcomes, regardless of whether the starting caesarean rate was already high (2). The healthcare professional can provide either elective or primary CS. Meanwhile, the overall women in these two studies were in the RC group 5, which means that all the women with previous CS were having a cephalic presentation. Unfortunately, Robson's classification did not subgroup women into more specific classification so that we can understand the main cause of maternal death.

Implementation of the Robson Classification may have limitations, mainly related to the availability and validity of information on the onset of labour and duration of pregnancy at delivery. One study proposed subdivision for the 10-group classification system according to augmentation or no augmentation, spontaneous/induced/CS before labour, with/without a previous uterine scar, previous or no previous vaginal delivery, and one or more than one previous scar (59). These subdivision systems for the group of women match with the group we use in this study (Robson classification group 5, 7, 8, 9, 10). Another study showed that groups 6–10 were smaller groups with high percentages of CS due to unavoidable obstetric indications (60). Therefore, group subdivision for the Robson Classification group is necessary. When compared with other studies internationally, almost all studies conveyed comparable results in groups 6–10. Using subgroup assessment for women with special needs and comorbidities or examining outcomes other than CS, especially hysterectomy, as part of a new system to monitor is recommended.

In summary, previous CS suggests higher risk and poorer clinical outcomes for women across a range of factors during and post pregnancy and birth. Conversely, and somewhat unexpectedly, other outcomes were not impacted or lowered. Hence, clinical impact and outcomes from repeated CS remain diverse and impacted by individual factors. Therefore, we recommend that health professionals must counsel women demanding a repeat CS in light of the findings of this meta-analysis and synthesis.

The current review and analysis have some methodological limitations, including that qualitative synthesis could be subjective. The data was extracted using only two databases and did not include unpublished work on the subject matter. Study heterogeneity may have affected the reliability of results. After we performed meta-regression that yielded the population size, year, and study design have no contribution to between-study heterogeneity, we did not perform the further analysis. We suggest future researchers explore the implications of elective CS, emergency CS and trial of labour on adverse maternal outcomes.

CONCLUSION

While recognising the benefits that CS can bring to reduce maternal mortality and perinatal outcomes, it needs to be recognised that these are yet to be realised in low- and middle-income countries. Additionally, there are increased risks for subsequent pregnancies, for both mother and child.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories

and accession number(s) can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

R-NA and UI designed the study. S-FW and W-SJ provided important feedback on the proposed study design. S-CC, AT, R-NA, and MH conducted the systematic literature search and quality assessment. AT, R-NA, and MH conducted the meta-analyses and the results were interpreted by all authors (SJ, S-CC, AT, R-NA, MH, DG, C-HC, S-FW, W-SJ, and UI). SJ and AT drafted the initial manuscript, which was thoroughly reviewed for important intellectual content and revised by all authors (S-CC, R-NA, MH, DG, C-HC, S-FW, W-SJ, and UI). All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

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Profile and Predictors of Maternal Quality of Life During Physiological Pregnancy: A Cross-Sectional Analysis

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Background: Quality of Life (QoL) and its determinants are significant in all stages of life, including pregnancy. The physical and emotional changes during pregnancy affect the QoL of pregnant women, affecting both maternal and infant health. Hence, assessing the QoL of pregnant women is gaining interest in literature. We, therefore, aimed to describe the QoL of pregnant women during physiological pregnancy and to identify its associated predictors in women attending a public healthcare institute of Quetta city, Pakistan.

Methods: A cross-sectional study was conducted at the Obstetrics and Gynecology Department of Sandeman Provincial Hospital Quetta city, Pakistan. The respondents were asked to answer the Urdu (lingua franca of Pakistan) version of the Quality of Life Questionnaire for Physiological Pregnancy. Data were coded and analyzed by SPPS v 21. The Kolmogorov–Smirnov test was used to establish normality of the data and non-parametric tests were used accordingly. Quality of Life was assessed as proposed by the developers. The Chi-square test was used to identify significant associations and linear regression was used to identify the predictors of QoL. For all analyses, $p < 0.05$ was taken significantly.

Results: Four hundred and three pregnant women participated in the study with a response rate of 98%. The mean QoL score was 19.85 ± 4.89 indicating very good QoL in the current cohort. The Chi-Square analysis reported a significant association between age, education, occupation, income, marital status, and trimester. Education was reported as a positive predictor for QoL ($p = 0.006$, $\beta = 2.157$). On the other hand, trimester was reported as a negative predictor of QoL ($p = 0.013$, $\beta = -1.123$).

Conclusion: Improving the QoL among pregnant women requires better identification of their difficulties and guidance. The current study highlighted educational status and trimester as the predictors of QoL in pregnant women. Health care professionals and policymakers should consider the identified factors while designing therapeutic plans and interventions for pregnant women.

Keywords: profile, predictors, maternal Quality of Life, physiological pregnancy, cross-sectional analysis

INTRODUCTION

Pregnancy and transition to motherhood is a wonderful experience. For a woman, where pregnancy brings self-fulfillment and indulgence, the fear of the upcoming events in life are also expected (1). As the pregnancy continues, women undergo physiologic, biochemical, and anatomic changes that develop anxiety, depression, and stress in expecting mothers (1). Moreover, motherhood demands adaptation to the intense transformations during the gestational period which is beyond women's control (2). Such changes result in the development of negative body image and dissatisfaction with life that is primarily attributed to the multiple stages of pregnancy (3, 4).

In today's world, the reproductive rights of women are assured in different public policies (5, 6). For that reason, quality of care and provision of services are hospital-centric and usually follow a medicalized and technocratic model (7). However, the least attention is given to non-clinical measures such as changes in mental health, self-esteem and confidence, and Quality of Life (QoL). Therefore, we strongly believe that in addition to standard pharmaceutical care, assessing the above-mentioned factors among pregnant women can provide a strong foundation for maternal health promotion (8).

Correlating, the QoL of pregnant women is influenced by several factors including social insertions, acceptance of gestation, restructuring families, the conception of the mother's role, and preparedness for childbirth during pregnancy (9). All these changes require a pregnant woman to adopt new responsibilities of motherhood. Although changes during the gestational period are short-term, they can remarkably affect the QoL of a pregnant woman (10). Within this context, the World Health Organization defines QoL as "*the position and perception of individuals in life, in the context of value systems and culture they live in with respect to their expectations, goals, concerns and standards*" (11). Moreover, QoL is also influenced by the physical health, psychological state, social relations, and relationship with important elements of the environment of the subject (12). Consequently, healthcare professionals in addition to traditional care must consider changes in QoL that are also supported by literature (13, 14).

In clinical and social research, QoL assessments are used for monitoring outcomes, and multiple instruments are used in literature that are either generic or disease-specific (15). Correlating, Barofsky concluded that definitions and assessment of a comprehensive concept of QoL change with time and objectivity (16). We do agree with this notion as precise methods of assessing QoL are missing in the literature and the ones used still have their limitations (17). Shifting our concerns to QoL in pregnancy, specific tools to assess QoL among pregnant women are least reported in the literature (18). To the best of our knowledge, although the generic WHOQOL-BREF is widely utilized to assess QoL of pregnant women (19), only one instrument i.e., QOL-GRAV is available to depict sensitive and accurate experiences during physiological pregnancy (18). Summarizing the opinions, the relationship between the physiological process of pregnancy and a woman's QoL is least discussed and reported in the literature and that was the major reason for the authors to conduct this study. Also, the study was conducted in a developing country where the QoL of pregnant women in primary care settings is neither reported nor given enough attention as an indicator of improving antenatal care. For that reason, we aimed to develop the profile and predictors of maternal QoL among pregnant women attending a primary healthcare institute of Quetta city, Pakistan.

METHODS

Study Design

A cross-sectional study was conducted at the Obstetrics and Gynecology Department of Sandeman Provincial Hospital Quetta (SPHQ), Pakistan. Sandeman Provincial Hospital was established in 1939 and is centrally located in the city. Being a public healthcare teaching institute, SPHQ is the facility of choice for most of the population. It has a well-established Obstetrics and Gynecology department with daily consultation of 500 patients per day (20).

Sample Size and Criteria

The sample size was calculated by the formula proposed by Daniel (21). By keeping the confidence level at 95%, response distribution of 50%, and margin of error at 5%, 377 respondents were calculated. To avoid missing data, a drop out of 10% was added and 414 respondents were conveniently approached for data collection.

Pregnant women attending the Obstetrics and Gynecology Department of SPHQ were approached by the first author. The respondents were informed about the nature of the research and their rights to confidentiality. Respondents not willing to participate, having mental disorders, and immigrants from other countries were excluded from the study.

Study Instrument

As discussed above, the only specific instrument available for the assessment of QoL in physiological pregnancy is the Quality of Life Questionnaire for Physiological Pregnancy (QOL-GRAV). The tool was developed by Vachkove et al., and the authors concluded that QOL-GRAV can sensitively and accurately capture the experiences of pregnant women that significantly affect their QoL (18). For assessment of QOL we used the validated version of QOL-GRAV-U (22). In addition to the QOL-GRAV-U, we also recorded the demographics of the respondents.

Ethical Approval

The Institutional Review Board of Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta approved the study [UoB/Reg/67]. In addition, written consent was also taken from the respondents before the data collection. The participants and attendants/care givers were informed about their rights of participation in the study and the right of withdrawal at any time without compromising their consultation at the healthcare institute.

Statistical Analysis

The data were coded and entered into SPPS v 21 for formal analysis. The Kolmogorov–Smirnov test was used to establish the normality of the data and non-parametric tests were used accordingly. Frequencies and percentages were used to explain the demographic variables. Quality of Life was measured as proposed by the developers (18). The Chi-square test was used to identify significant associations and linear regression was used to identify the predictors of QoL. For all analyses, $p < 0.05$ was taken significantly.

RESULTS

Demographic Characteristics of Study Respondents

Four hundred and three pregnant women participated in the study with a response rate of 98%, whereas 11 participants were dropped out due to the reason that 5 questionnaires had duplicate responses and 6 questionnaires were incomplete. The description of socio-demographic variables and frequency distribution of the respondents are summarized in **Table 1**. Most of the participants were in age range of 26–35 years (241, 59.8%). Ninety were illiterate, and the cohort was dominated by housewives (75.9%). The majority (91%) had rural residencies and 60.3% were in their second trimester.

TABLE 1 | Demographic characteristics of study respondents.

Characteristics	Frequency	Percentage
Age		
15–25	116	28.8
26–35	241	59.8
36–45	46	11.4
Education		
Illiterate	90	22.3
Metric	71	17.6
Intermediate	84	20.8
Graduation	71	17.6
Post-graduation	87	21.5
Occupation		
Housewife	306	75.9
Working women	97	24.1
Income [Pakistan Rupees= Pk. Rs.]		
None	306	75.9
<10,000	30	7.4
11,000–20,000	31	7.7
>20,000	36	8.9
Marital status		
Widowed	5	1.2
Married	398	98.8
Locality		
Urban	35	8.7
Rural	368	91.3
Trimester		
1	92	22.8
2	243	60.3
3	68	16.8
Number of children		
0	10	2.5
1–3	144	35.7
4–6	130	32.3
>6	119	29.5
Husband's education level		
Illiterate	79	19.6
Metric	51	12.7
Intermediate	78	19.4
Graduation	90	22.3
Post-graduation	105	26.0
Husband's occupation		
Government employee	111	27.5
Private employee	194	48.1
Business	98	24.4

Assessment of Quality of Life

The QOL-GRAV-U is a 9-item questionnaire where three items out of nine [item 7, 8, and 9] are reverse coded and are presented in a 5-point Likert format. The Likert rating of 1 represents the best and 5 the worst state of QoL. Lower mean scores reflect high QoL and vice versa. According to the developers, QoL is measured as excellent [mean score of 9–18], very good [mean score of 19–27 points], good [mean score of 28–36 points], and not very good [man score of 37–45 points]. In the current study, the mean QoL score was 19.85 ± 4.89 indicating very good QoL in the current cohort (**Table 2**).

Association Between Demographic Variables and Quality of Life

Table 3 presents the cross-tabulation analysis between socio-demographic and study variables. For this analysis, we categorized QoL into good and poor [mean values of >22 as poor and <22 as good QoL]. The Chi-Square analysis reported a significant association between age, education, occupation, income, marital status, and trimester. The interpretation of the significant values reported a moderate strong relationship hence confirming the possibility of linear regression analysis (23). No significant association was reported among other variables.

Predictor of Quality of Life Among Study Respondents

A simple linear regression was carried out to identify the predictors of QoL in the current cohort. The variables that were significantly associated with QoL were entered into the regression model. The scatter plot showed that there was moderate to strong positive linear relationships between the variables which was confirmed with acceptable Pearson's correlation coefficient (>0.40). Results of the multiple linear regression indicated that there was a collective significant effect between the dependent and independent variables [$F_{(6,94)} = 20.82$, $p < 0.001$]. Furthermore, the predictors managed to explain 55.5% of the variance ($R^2 = 0.55$). Education was reported as a positive predictor for QoL ($p = 0.006$, $\beta = 2.157$) indicating that for

TABLE 2 | Quality of Life of the study respondents.

Items in questionnaire	Not at all, *N* (%)	A little, *N* (%)	A middle, *N* (%)	A lot, *N* (%)	Maximally, *N* (%)
To what extent do you feel that your physical changes associated with this pregnancy do not allow you to do what you need?	119 (29.5)	192 (47.6)	42 (10.4)	41 (10.2)	9 (2.2)
To what extent do you feel that your psychological changes associated with this pregnancy do not allow you to do what you need?	153 (38.0)	159 (39.5)	51 (12.7)	31 (7.7)	9 (2.2)
How worried are you about not being able to handle household chores?	104 (25.8)	119 (29.5)	109 (27.0)	51 (12.7)	20 (5.0)
How worried are you about carrying out the pregnancy successfully?	152 (37.7)	83 (20.6)	51 (12.7)	75 (18.6)	42 (10.4)
How worried are you about not being able to handle labor and delivery?	72 (17.9)	109 (27.0)	74 (18.4)	86 (21.3)	62 (15.4)
Have you been forced to cut down on your physical activity during this pregnancy?	70 (17.4)	90 (22.3)	142 (35.2)	85 (21.1)	16 (4.0)
How satisfied are you with your partner now?	2 (0.5)	5 (1.2)	52 (12.9)	126 (31.3)	218 (54.1)
How satisfied are you with your social life now?	3 (0.7)	11 (2.7)	57 (14.4)	173 (42.9)	159 (39.5)
How satisfied are you with how you manage to adapt to this pregnancy?	24 (6.0)	20 (5.0)	46 (11.4)	134 (33.3)	179 (44.4)

Based on the total score, the QoL was evaluated as excellent (9–18 points), very good (19–27 points), good (28–36 points), not very good (37–45 points). Mean Quality of Life score in current cohort was 19.85±4.89 indicating very good Quality of Life in the current cohort.

every 1 unit increase in education, there is a possibility that QoL will increase by 2.157 times. On the other hand, trimester was reported as a negative predictor of QoL ($p = 0.013$, $\beta = -1.123$) indicating that as trimester increases, QoL decreases by 1.123 as shown in **Table 4**.

DISCUSSION

Over the past decades, the assessment of QoL in both clinical and non-clinical settings have gained immense significance. Accordingly, different assessment tools were developed to measure psychological, physical, and social QoL among patients and the general population. However, in comparison to other conditions maternal QoL is least studied in the literature. A possible reason is attributed to the lack of established measures while assessing QoL in pregnant women (18). As a result, the current study was aimed to highlight predictors of maternal QoL in pregnant women of Quetta City, Pakistan. We also did an extensive literature review, and it was revealed that only a few studies report QoL of pregnant women but not from Pakistan.

Our study involved a cohort of 403 pregnant whereby 59% of the respondents were in the age range of 25–35 years. Other studies conducted in Brazil and China also highlighted the similar age group i.e., 26 ± 6.4 and 27.3 ± 4.0 years, respectively (24, 25). The marital status and occupation of women were also like what is reported in Iran (26). However, the other demographics were inconsistent with studies where the literacy rate was higher (24). Large numbers of our respondents (91.3%) were from rural areas and [60.3%] were in the second trimester of pregnancy, unlike the results from a study conducted in France (27). A The possible reason of this differentiation is attributed to the cultural context, marriage age, and practices that vary differently in Pakistan and other regions (especially the developed world).

The mean QoL scores of the current study respondents were 19.85 ± 4.89 which indicated very good QoL. Our results are parallel to what was reported by studies conducted in Serbia and Slovenia (28, 29). The gestational period has a direct relationship with QoL, and this serves as an indicator for health care professionals to take measures for improving QoL (30). Although QoL in the current cohort was promising, we still advocate the provision of special attention and care to pregnant women with poor QoL.

Our study managed to identify various significant relationships between demographics and QoL (**Table 3**). The published literature does support our results and has established relationships between QoL and demographic characteristics of pregnant women. Age was significantly associated with the maternal QoL in a study conducted by Balíková and BuŽgová in which women of age >29 years had low QoL as compared to younger women (31). In line with what is being discussed; Mazúchová et al. reported the best QoL in younger women when compared with middle-aged women and was worst in the older age group (29). Correspondingly, women with higher educational backgrounds had better QoL (32). We also found that period of pregnancy was also significantly associated with maternal QoL agreeing with the findings of Mazuchova et al. The authors found that the best QoL score was in the first trimester and least in the second trimester of the pregnancy (29). A positive relationship between household income and QoL was also reported (33). However, studies also discovered that there was no relation between QoL and monthly income. This difference is understandable, and the majority of the respondents do not tend to disclose their financial status (32).

A simple linear regression was carried out to identify the predictors of QoL. The variables that were significantly associated with QoL were entered into the regression model. Education was reported as a positive predictor for QoL indicating that for every 1 unit increase in education, QoL improves by 2.157 times. In connection to our findings, a study conducted in Thailand on older pregnant women concluded that education had a direct link with QoL, and women with higher educational status had better QoL (34). A study conducted in Iran revealed that women with higher education status had better QoL than other women (32). Education plays a key role in improved awareness of medical

TABLE 3 | Patients' demographics characteristics and Quality of Life.

Characteristics	Quality of Life		*P*-value*	*R*-value
	Good	Poor		
Age				
15–25	67 (29.9)	49 (27.4)	0.004 ($\phi c = 0.386$)	0.352
26–35	129 (57.6)	112 (62.6)		
36–45	28 (12.5)	18 (10.1)		
Education				
Illiterate	44 (19.6)	46 (25.7)	0.002 ($\phi c = 0.386$)	0.419
Metric	37 (16.5)	34 (19.0)		
Intermediate	51 (22.8)	33 (18.4)		
Graduation	42 (18.8)	29 (16.2)		
Post-graduation	50 (22.3)	37 (20.7)		
Occupation				
Housewife	180 (80.4)	126 (70.4)	0.014 ($\phi c = 0.386$)	0.377
Working women	44 (19.6)	53 (29.6)		
Income				
None	178 (79.5)	124 (69.3)	0.005 ($\phi c = 0.286$)	0.399
<10,000	8 (3.6)	22 (12.3)		
11,000–20,000	19 (8.5)	12 (6.7)		
>20,000	19 (8.5)	21 (11.7)		
Marital status				
Widowed	0 (0)	5 (2.8)	0.017 ($\phi c = 0.312$)	0.310
Married	224 (100.0)	174 (97.2)		
Locality				
Urban	20 (8.9)	15 (8.4)	0.496	0.214
Rural	204 (91.1)	164 (91.6)		
Trimester				
1	39 (17.4)	53 (29.6)	0.014 ($\phi c = 0.304$)	0.425
2	146 (65.2)	97 (54.2)		
3	39 (17.4)	29 (16.2)		
Number of children				
0	5 (2.2)	5 (2.8)	0.271	0.214
1–3	78 (34.8)	66 (36.9)		
4–6	81 (36.2)	49 (27.4)		
> 6	60 (26.8)	59 (33.0)		
Husband's education level				
Illiterate	43 (19.2)	36 (20.1)	0.262	0.118
Metric	24 (10.7)	27 (15.1)		
Intermediate	44 (19.6)	34 (19.0)		
Graduation	97 (43.3)	67 (37.4)		
Post-graduation	16 (7.1)	15 (8.3)		
Husband's occupation				
Government employee	57 (25.3)	55 (30.7)	0.385	0.009
Private employee	111 (49.3)	83 (46.4)		
Business	57 (25.3)	40 (22.3)		

**Chi square, all entries in bold are significant and values in the brackets are the interpretation of the significant values. R represents the correlation values.*

TABLE 4 | Factor associated with Quality of Life among pregnant women.

Model	Standardized coefficients β	*t*	Sig.	95% confidence interval	
				Lower bound	Upper bound
(Constant)		10.693	0.000	19.006	27.569
Age	0.045	0.911	0.363	−0.417	1.136
Education	2.157	2.759	***0.006***	0.906	0.152
Occupation	0.062	0.583	0.560	−1.684	3.106
Income	0.163	1.454	0.147	−0.280	1.869
Marital status	−0.055	−1.112	0.267	−6.669	1.850
Trimester	−1.123	−2.500	***0.013***	−1.705	−0.204

Bold and italic values represents significant associations.

facilities, utilization of healthcare services and understanding of the needs and demands of pregnancy. Educated women are also in a position of getting job offers and can get employment easily as compared to housewives and less educated. Our claims are supported by studies whereby employed pregnant women had improved QoL as job satisfaction and financial stability establish greater self-esteem (9, 10). Concluding, women with higher education have higher self-efficacy and are anticipated to receive encouraging social support therefore have improved QoL.

On the other hand, trimester was reported as a negative predictor of QoL indicating that as trimester increases, QoL decreases by 1.123 times. Zarei et al. also reported similar findings and highlighted gestational age as a negative predictive factor for maternal QoL (26). Zahedi et al., also claimed that with the increase in gestational age, mean scores of QoL decreases. The authors also reported that the maximum score of QoL was found in the first trimester and lowest in the third trimester (35). Conversely, Makvandi et al. did not find any relationship between QoL and gestational age (36). As per our results, best QoL was reported in the first trimester and is attributed to the feeling of parity and happiness of motherhood. In addition, fatigue, nausea, and vomiting starts as pregnancy continues and that decreases QoL. Finally, worse QoL in the third trimester is attributed to an increase in weight, reduced sexuality, and sleep disorders.

Summarizing our results, QoL was very good in most of our respondents. The findings of this study will assist health care professionals in establishing interaction and resolving associated problems that affect QoL during pregnancy. Pregnant women are influenced by various bio-psycho-social factors therefore, it is essential to have a care plan that fulfills the actual needs of this group during the gestational period.

CONCLUSION

Improving the QoL among pregnant women requires better identification of their difficulties and guidance. Therefore, frequent assessment of QoL, including its dimensions, of pregnant women can clarify women's health status. In this context, results of this study identified some predictors of QoL that can provide insights for better understanding of factors affecting QoL. Because educational status and trimester appeared

as predictors of QoL, healthcare professionals should consider the identified factors while designing therapeutic plans or planned interventions for pregnant women. Despite the positive results, it is crucial to screen the Quality of Life of pregnant women and to pay special care to pregnant women who have a lower Quality of Life.

STRENGTHS AND LIMITATIONS

Relationship between pregnancy and woman's QoL is least reported in the literature. Therefore, the current study is pioneer study from Pakistan.

The study was conducted in the Quetta city of Pakistan, which is not representative of the whole country. A comprehensive study is recommended throughout the country to generalize the result. We also recommend that pregnant women visiting private healthcare institutes should be added into the study to underline possible differences of QoL between public and private healthcare facilities.

FUTURE RECOMMENDATIONS

The study was single cantered, consequently targeting other public and private healthcare institutes may bring diversity of findings. Moreover, assessing QOL in specific trimesters can also bring interesting outcomes. Therefore, a study on different healthcare settings with individualized trimesters is hereby recommended.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Faculty of Pharmacy & Health Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RI, MS, NB, and AS conceptualized and designed the study. AR, SR, FB, and SH collected the data while ZH, FS, and NA analyzed and interpreted the data. The study was supervised by FS, QI, and AHK. All authors have met the criteria for authorship and had a role in preparing the manuscript and also, approved the final manuscript.

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Assessment of Knowledge, Attitude, and Practice of Obstetricians and Gynecologists Toward Off-Label Medicine Use in Female Reproductive Health Issues

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Background: Off-label medication usage (OLMU) is prevalent in the treatment of various diseases, including female reproductive health issues (FRHIs). However, there is a paucity of literature on the perspective of health professionals on this subject. The purpose of the current study was to assess gynecologists/obstetricians' knowledge, attitude and practice toward OLMU in the treatment of FRHIs.

Methods: The current cross-sectional study was conducted in September and October 2021, at five tertiary care hospitals (two public and three private sector), different clinics and maternity homes in a metropolitan city of Karachi, Pakistan. The target population was gynecologists, obstetricians and physicians/residents working in the ob/gyn department in various hospitals and clinical settings of Karachi.

Results: The overall response rate was 77.1%. The mean age of the study respondents was 36.1 ± 7.7 years; $n = 85$ (55.9%) respondents were working in primary patient care. The majorly reported OLMU by the respondents were clomiphene citrate in unexplained infertility ($n = 66$; 43.4%), metformin to improve cycle regularity in females with polycystic ovary syndrome (PCOS) ($n = 59$; 38.8%) and letrozole to induce ovulation ($n = 31$; 20.4%). The majorly stated categories of OLMU were at a different dose ($n = 95$; 62.5%) and at different indications than approved to treat ($n = 89$; 58.5%). It was reported by the majority of the respondents ($n = 95$; 62.5%) that they do not follow any guidelines or regulations for OLMU in their work setting; however, the response was statistically varied with the working organization (CI 2.14–2.93; $p = 0.037$) and practice area (CI 2.85–4.32; $p = 0.0001$) of respondents.

Conclusions: The present study revealed that the respondents were well-familiar with the practice of OLMU in the treatment of FRHIs. They expressed their concerns about decreasing such practices by being involved in collective decision-making procedures, and they were inclined to accept initiatives aimed at ensuring drug safety in patients.

Keywords: off-label prescribing, female reproductive health, gynecologists/obstetricians, Pakistan, knowledge

INTRODUCTION

The reproductive health of a woman is vital to her overall wellbeing. Reproductive health is described as a condition of physical, emotional, mental, and social wellbeing in all aspects of reproduction, rather than simply the absence of sickness, malfunction, or infirmity (1). Menstrual health, which marks the beginning of reproductive health, and menopause, which marks the end of reproductive health, are two frequently overlooked aspects. Likewise, female infertility affects millions of couples worldwide, and there are several drugs available to help with conception (1). In general, infertility is defined as the inability to conceive (get pregnant) after 1 year (or more) of unprotected sex. Since women's fertility declines progressively with age, some providers analyze and treat women aged 35 and above after 6 months of unprotected sex (1). Fertility therapies include hormone and ovulation-regulating medicines, occasionally combined with minor surgical interventions, and are evaluated by the Food and Drug Administration (FDA) to get a license for a specific mode of application. Many of the medications given to treat female infertility are used off-label, which means they have not passed all of the tests required for approval for a specific purpose (2).

Off-label medication usage (OLMU) is defined as prescribing medicines in a way that contradicts product usage information issued by regulatory authorities. OLMU can be grouped into several categories, including unapproved indications, use in a specific demographic, administration by an unauthorized method, and administration at a dose not mentioned in the FDA-approved label (2). OLMU has increased significantly across all medical specialties in preceding decades because it allows the prescribers to employ novel treatment alternatives based on the most recent data. The majority of medications used to treat FRHIs are used off-label (3). Misoprostol can be used to treat both early (miscarriage) and late pregnancy loss. Its extensive usage for the treatment of first-trimester miscarriage is strongly supported by high-quality evidence from throughout the world (4). Metformin is used therapeutically off-label in the treatment of hirsutism, acne, and insulin resistance in PCOS, despite conflicting data regarding anti-androgenic properties. Metformin can also be taken alone or in conjunction with clomiphene citrate to enhance ovulation in women with PCOS (3). Off-label usage of letrozole for ovarian stimulation and ovulation induction in anovulatory and unexplained infertility. Bromocriptine is a dopamine agonist that is used off-label in the treatment of pituitary origin infertility and ovarian hyperstimulation syndrome (OHSS) (3).

The legislation governing the use of off-label drugs has not been unified globally. The suitability of OLMU stays a matter of discussion, due to their susceptibility regarding the proven medical benefits and probable toxicities, little or no evidence to assist in scientific decision-making, increased treatment expenses for patients and ethical concerns (5). National legislation, rules, or recommendations regulating OLMU have been created in certain developed nations, such as the United Kingdom, France, and the United States, and rational OLMU is permitted in these countries (6). As per the "Amendments to the Indian Medical Council Act," the off-label prescription is banned in India (7). However, according to drug regulations in Pakistan, there is no clear explanation of off-label prescription practices.

The scarcity of controlled clinical trials in vulnerable patients is the key factor for the common practice of OLMU. Many physicians consider that OLMU has a significant role in therapeutic practice representing the optimum way to utilize that treatment and OLMU is frequently required when treating certain patients, such as those whose symptoms have proved resistant to a variety of therapeutic options (8). OLMU may be beneficial in some cases because it provides evidence-based therapeutic alternatives to patients who have no other options, such as in situations where no authorized medications exist or for patients who have used the typical empiric treatment. Though OLMU may be therapeutically justifiable in some cases, it is connected with a variety of safety and ethical concerns (8). OLMU can affect the patient wellbeing in circumstances when a benefit-risk ratio has not been completely established. This is mostly because OLMU is generally not evaluated by regulators, guidance developers, or even healthcare legislators (9). When carefully evaluated, certain regularly practiced OLMU have likewise been revealed to be either hazardous or useless (10). The expert consensus that for safe use of OLMU they must be based on supportive evidence and being approved by the ethics or formulary committee (11). Besides the informed consent must be obtained from the patient and adverse drug reactions (ADRs) should be monitored and regularly updated in a database of off-label drugs (12).

Previous studies shown that the healthcare experts emphasize that OLMU has a significant role in therapeutic practice, but they likewise acknowledge that using an OLMU might increase the risk of claims if a patient has unfavorable or severe adverse responses (13, 14). In Pakistan, being a developing country, the economic burden of OLMU could further deteriorates the situation and therefore it is imperative to study this issue in the local context. Several studies have been conducted on the health professionals' insight regarding OLMU in different medical conditions; nevertheless, to the best of our knowledge,

no such work has been published regarding the OLMU in the treatment of female reproductive health issues (FRHIs) (8, 9, 12, 14). Hence, the purpose of the current study was to assess gynecologists/obstetricians' knowledge, attitude and practice toward OLMU in the treatment of FRHIs.

METHODOLOGY

Study Design and Setting

A survey based quantitative cross-sectional study was conducted in September and October 2021, at five tertiary care hospitals (two public and three private sector), different clinics and maternity homes in a metropolitan city of Karachi, Pakistan. The target population was gynecologists, obstetricians and physicians/residents working in the ob/gyn department in various hospitals and clinical settings of Karachi and willing to participate in the study. The questionnaire were distributed through email or personal contacts and the respondents were invited to complete the survey form. A reminder email was sent to those who had not responded after a week to get the maximum response rate.

Ethical Approval

The study was conducted as per the recommendations of the "Declaration of Helsinki" and the approval was obtained from the Ethical Review Committee of Sohail University with the protocol # 000125/21. The written consent was obtained from the respondents before the study and the goals of the study were explained to them.

Sampling Technique

The study sample size was calculated by G Power software, version 3.0.10 (15), by using Chi-square goodness of fit test with an effect size of 0.2, alpha error 0.05, and power of test 0.8 (8); the calculated sample size was found to be 197. The convenient and snowball sampling techniques were used to select the respondents.

Research Instrument Development and Piloting

The questionnaire was derived from a review of prior studies (3, 12, 16–18). In addition to the demographic information the study questionnaire had four sections:

- The first section had five closed ended questions with "true," "false," and "do not know" options designed to evaluate the respondents' awareness of OLMU in the treatment of FRHIs, their concerns about its safety and efficacy, and the possibility of ADRs when taking OLMU.
- The second section consists of 15 closed ended questions designed to assess respondents' current practice of prescribing different categories of OLMU in the treatment of FRHIs, their proclivity to prescribe OLMU and perceived barriers. The items were scored on a 5-point Likert scale, ranging from strongly agree = 5 to strongly disagree = 1.
- The third section consists of five closed ended questions with "yes" or "no" options about their practice of obtaining informed, written/verbal agreement from patients before prescribing OLMU in the treatment of FRHIs.
- The fourth section consists of five closed ended questions enquiring about the respondents' knowledge sources and examining their ideas for minimizing such practices.

The face validity and content validity of the questionnaire was subjected by three gynecologists working in Dow University Hospital. As per the experts' recommendations, minor adjustments were made to the final version of the questionnaire. The piloting of the research questionnaire was conducted on 20 gynecologists and the research questionnaire was validated. The Cronbach-alpha test was conducted to verify the questionnaire's reliability and internal consistency. The dependability coefficient was 0.733, which was within an acceptable range.

Data Collection and Analysis

The data entry and analysis of responses collected were done by the Statistical Package for Social Sciences v.20.0 (SPSS; Chicago, IL). The demographic data of the respondents were illustrated as percentages and frequencies. The Shapiro-Wilk test was performed to establish the normality of the variables. Pearson-correlation coefficients and analysis of variance were employed to identify the relationship between the independent variables and the responses considering p-values <0.05 as statistically significant.

RESULTS

Demographic Information

In the current research, 152 gynecologists, obstetricians and physicians/residents completed the survey; hence, the overall response rate was 77.1%. Only $n = 9$ (5.9%) were males and $n = 143$ (94.0%) were females. The mean age of the study respondents was 36.1 ± 7.7 years with $n = 85$ (55.9%) were working in primary patient care. The respondents $n = 52$ (34.2%) whereas $n = 48$ (31.5%) were having a working experience of 6–10 and 1–5 years, respectively. **Table 1** depicted the detailed demographics of the study population.

Respondents' Knowledge and Attitude Toward OLMU

The respondents $n = 120$ (78.9%) were well-familiar with the concept of OLMU and $n = 70$ (46.1%) had heard about the OLMU during their professional life. However, their knowledge was found to be statistically significant with their practice area ($p = 0.0001$). On inquiring about the safety of OLMU, around 60% of respondents considered them safe if used with appropriate scientific evidence (**Figure 1**). The respondents $n = 108$ (71.1%) consider that there is no meaningful difference between the on-label and OLMU in terms of quality, safety and efficacy. This opinion was varying significantly with the experience ($p = 0.017$) and practice area ($p = 0.025$) of respondents. Around 70% of the respondents showed their concerns when prescribing OLMU about its safety and efficacy in the treatment of female infertility and consider that some OLMU could increase the likelihood of

TABLE 1 | Respondents' demographic characteristics.

Baseline characteristics	Frequency (%)
Gender	
Male	9 (5.9)
Female	143 (94.0)
Working organization	
Private	112 (73.6)
Public	40 (26.3)
Working experience	
<1 year	13 (8.5)
1–5 years	48 (31.5)
6–10 years	52 (34.2)
11–20 years	33 (21.7)
More than 20 years	6 (3.9)
Practice area	
Primary patient care	85 (55.9)
Secondary patient care	31 (20.3)
Tertiary patient care	36 (23.6)

ADRs. However, around 85% stated that have not observed any ADR when using OLMU in their practice.

Respondents' Perceived Reasons of Practicing OLMU

More than half of the respondents ($n = 84$; 55.2%) consider that the OLMU allows for innovation in healthcare practice, especially when recognized therapies have failed; however, the response was varied with the working experience (CI 2.21–2.73; $p = 0.003$) and practice area (CI 2.28–3.52; $p = 0.005$) of respondents. The respondents ($n = 80$; 52.6%) think that the OLMU provides clinicians with early access to potentially useful drugs, as well as the ability for professionals to adopt new procedures based on developing evidence; however, the response was varying significantly with the working organization of respondents (CI 2.42–2.93; $p = 0.001$). The respondents perceived major reasons for increased use of OLMU in the treatment of FRHIs were availability of only a few FDA-approved drugs ($n = 34$; 22.3%) and FDA-approved drugs are too expensive or otherwise inaccessible ($n = 33$; 21.7%) (**Figure 2**). The respondents ($n = 97$; 63.8%) consider that the symptoms frequently cross over from one illness state to the next, prompting clinicians to utilize drugs for unapproved gynecological indications; the response varying significantly by the working organization (CI 2.12–2.65; $p = 0.05$) and practice area of the respondents (CI 2.17–3.24; $p = 0.004$).

Commonly Used Categories of OLMU in Practice of Respondents

The respondents were inquired about the category of OLMU that is most commonly used in their practice (**Figure 3**). The majorly reported OLMU by the respondents were clomiphene citrate as an infertility treatment in males ($n = 66$; 43.4%), metformin to improve cycle regularity in females with polycystic ovary syndrome (PCOS) ($n = 59$; 38.8%) and letrozole to induce ovulation ($n = 31$; 20.4%). The majorly stated off-label prescribing were at a different dose than the one it is approved to treat ($n = 95$; 62.5%) and at different indications than the one it is approved to treat ($n = 89$; 58.5%). **Figure 4** depicted the factors which can be more beneficial in reducing the OLMU. The majorly reported factors were increasing the number of clinical trials for new drugs in infertility patients ($n = 55$; 36.1%) and making more appropriate formulations available for infertility patients ($n = 37$; 24.3%).

Respondents' Practice of Informing Their Patients About OLMU

Around 40% of the respondents informed their patients when prescribing an OLMU whereas more than 75% did not request informed, written consent/verbal consent from patient or attendant before prescribing OLMU. The respondents ($n = 91$; 59.9%) think that physician who is prescribing the off-label has the main responsibility to inform the patient about OLMU to treat them. The majority of the respondents ($n = 104$; 68.4%) agreed that it would needlessly worry the patient if we told them that medicine that she was being treated with was used in an off-label manner. The respondents ($n = 95$; 62.5%) agreed that the benefits associated with OLMU outweigh the associated risk whereas ($n = 91$; 59.6%) consider that OLMU has the potential to become widely accepted in clinical practice and to become the standard therapy for treating different female reproductive health issues.

Respondents' Perceived Barriers for OLMU and Their Reliable Sources of Information

The majority of the respondents ($n = 115$; 75.6%) deemed that the healthcare professionals risk legal liability if they use OLMU in patient care, especially if the patient develops an ADR. It was reported by the majority of the respondents ($n = 95$; 62.5%) that they do not follow any guidelines or regulations for OLMU in their working hospital; however, the response was found to be statistically associated with the working organization (CI 2.14–2.93; $p = 0.037$) and practice area (CI 2.85–4.32; $p = 0.0001$) of respondents. The respondents' perceived majorly reported ADRs of fertility drugs were ectopic pregnancy ($n = 29$; 19%), Ovarian Hyperstimulation Syndrome (OHSS) ($n = 25$; 16.4%) and having multiples ($n = 22$; 14.5%). The majority of the respondents ($n = 102$; 67.1%) stated that they were not familiar with how to cope with the side effects of fertility drugs. The respondents' major sources of information were colleague/peer recommendation (43%), previous experience with the drug (18%) and medical journals (13%) (**Figure 5**).

DISCUSSION

The world's population is facing enormous challenges due to reproductive issues; with an obvious concern of fertility issues and a declining birth rate (3). Numerous endogenous and exogenous variables have an impact on female reproductive health. Many FRHIs are becoming more prevalent due to the increased release into the environment of industrial chemicals

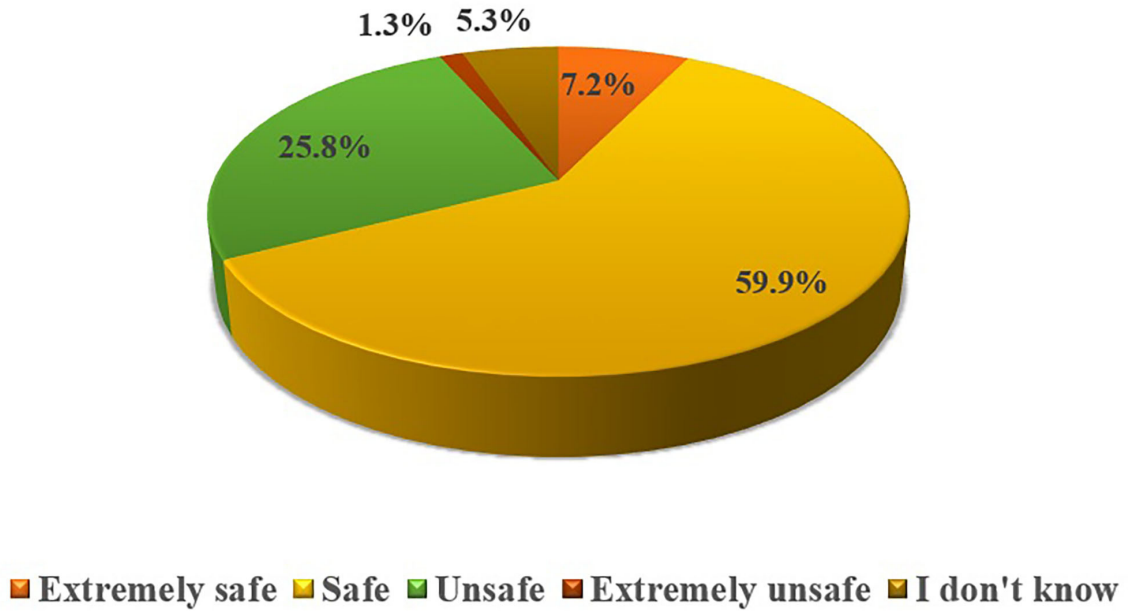

FIGURE 1 | Respondents' attitude toward OLMU safety in the treatment of female reproductive health issues.

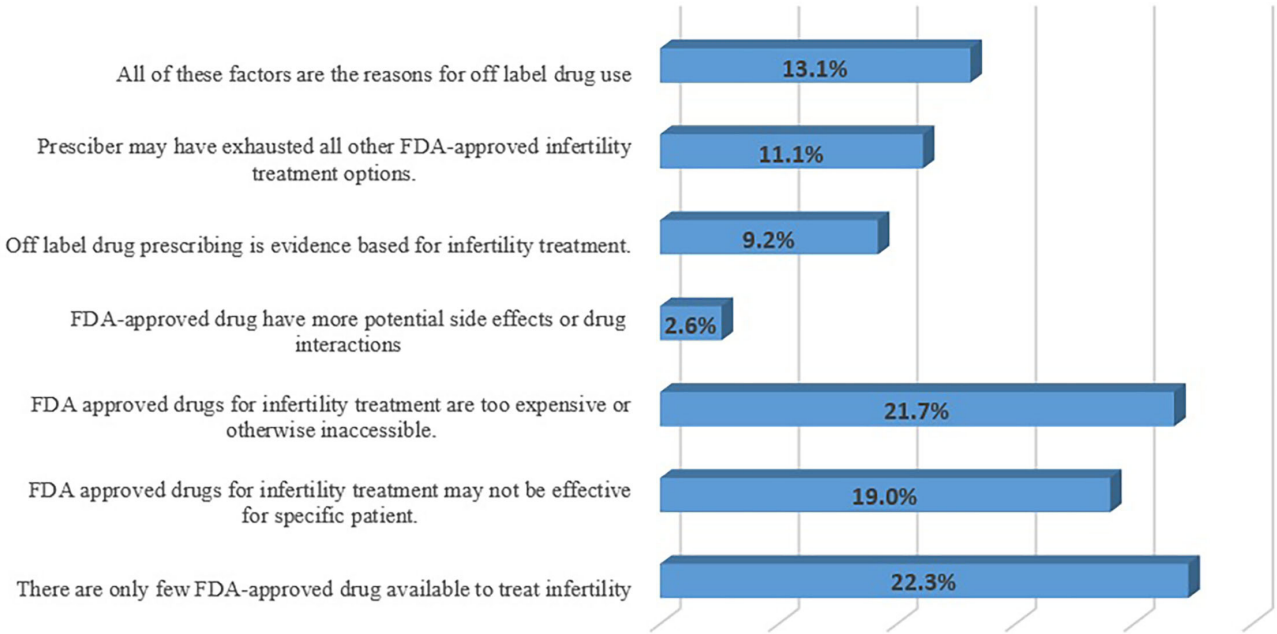

FIGURE 2 | Respondents' perceived major reasons for increased use of OLMU.

with analogous properties, and many of these substances have been documented as entering the human body via urine or blood (1, 2). As far as we possibly know, this is the first study conducted in a Pakistani setting on gynecologists/ obstetricians' knowledge, attitudes, and practices related to the use of OLMU. The outcomes of the current study revealed considerable understanding of OLMU among the respondents as they were found to be well-aware with the concept. Other studies indicated the parallel findings depicting the major reasons for awareness of OLMU among healthcare professionals were their post-graduate and undergraduate teaching and practical exposure (18, 19). The majorly reported OLMU by the respondents were clomiphene

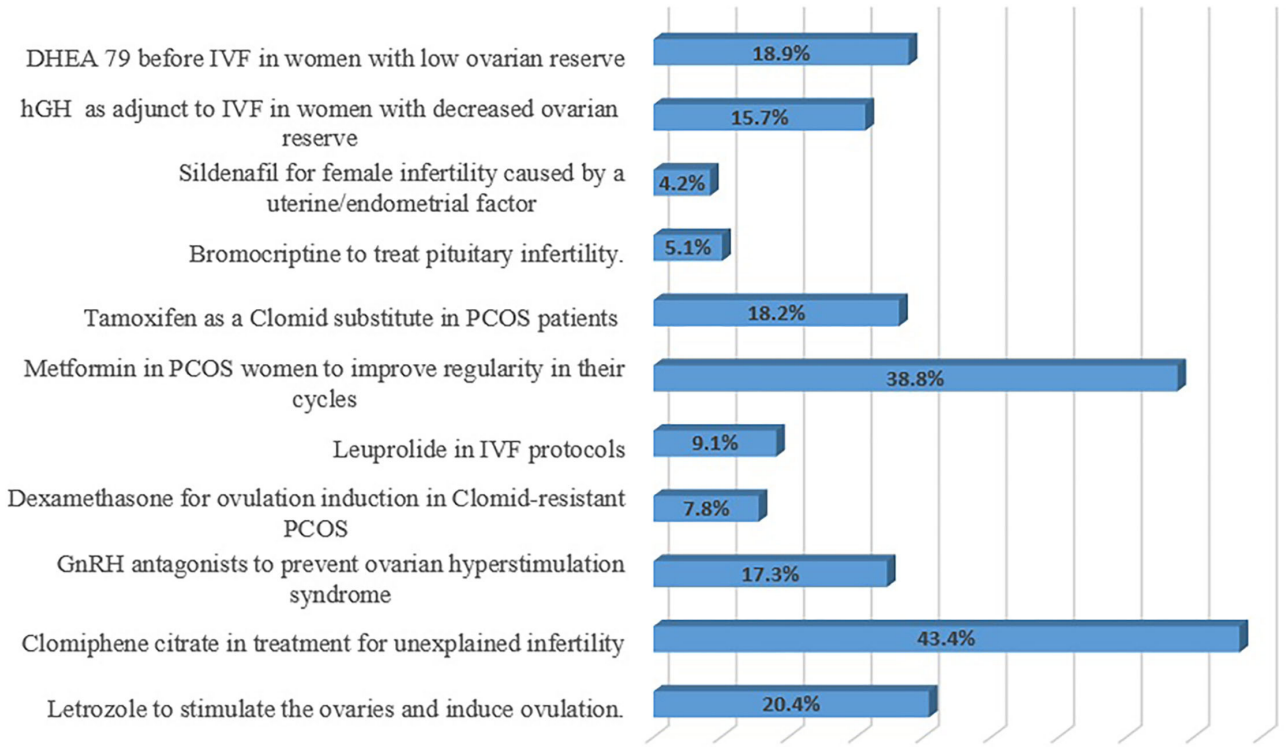

FIGURE 3 | Respondents' most commonly used category of OLMU in their practice. GnRH, Gonadotropin-releasing hormone; IVF, *In vitro* fertilization; PCOS, Polycystic ovary syndrome; hGH, Human growth hormone; DHEA, Dehydroepiandrosterone.

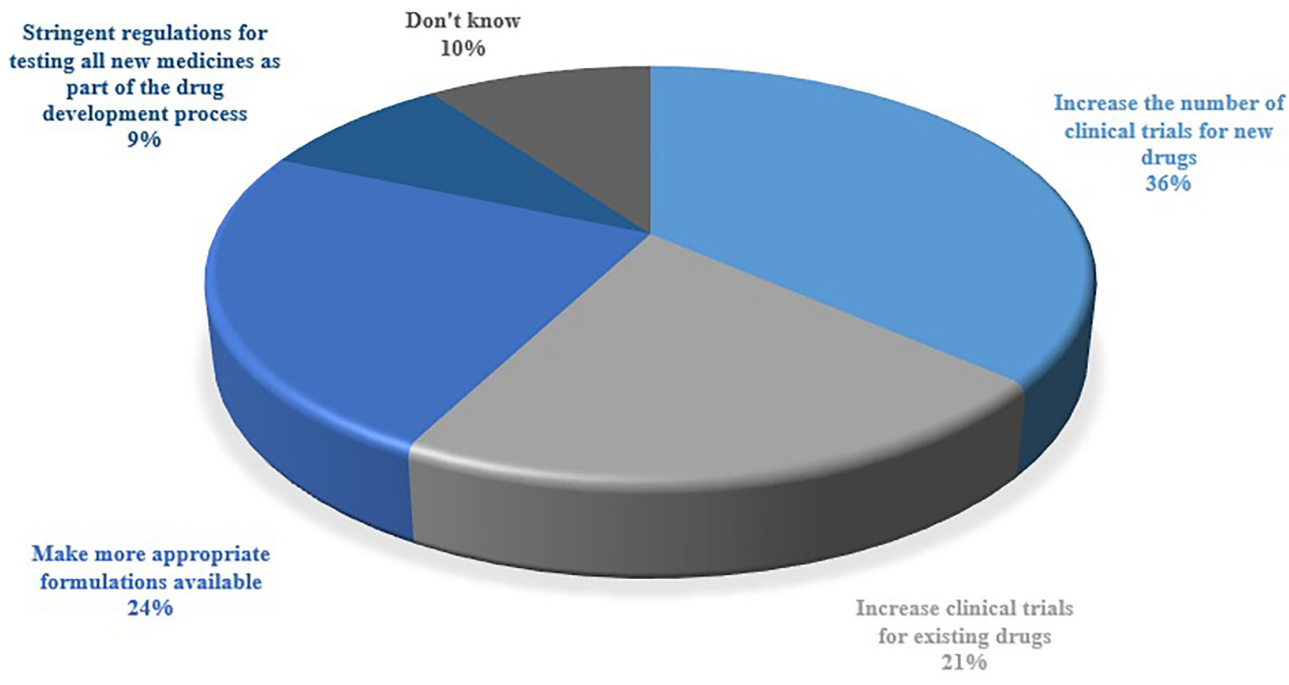

FIGURE 4 | Respondents' perceived beneficial factors in reducing the OLMU for infertility treatment.

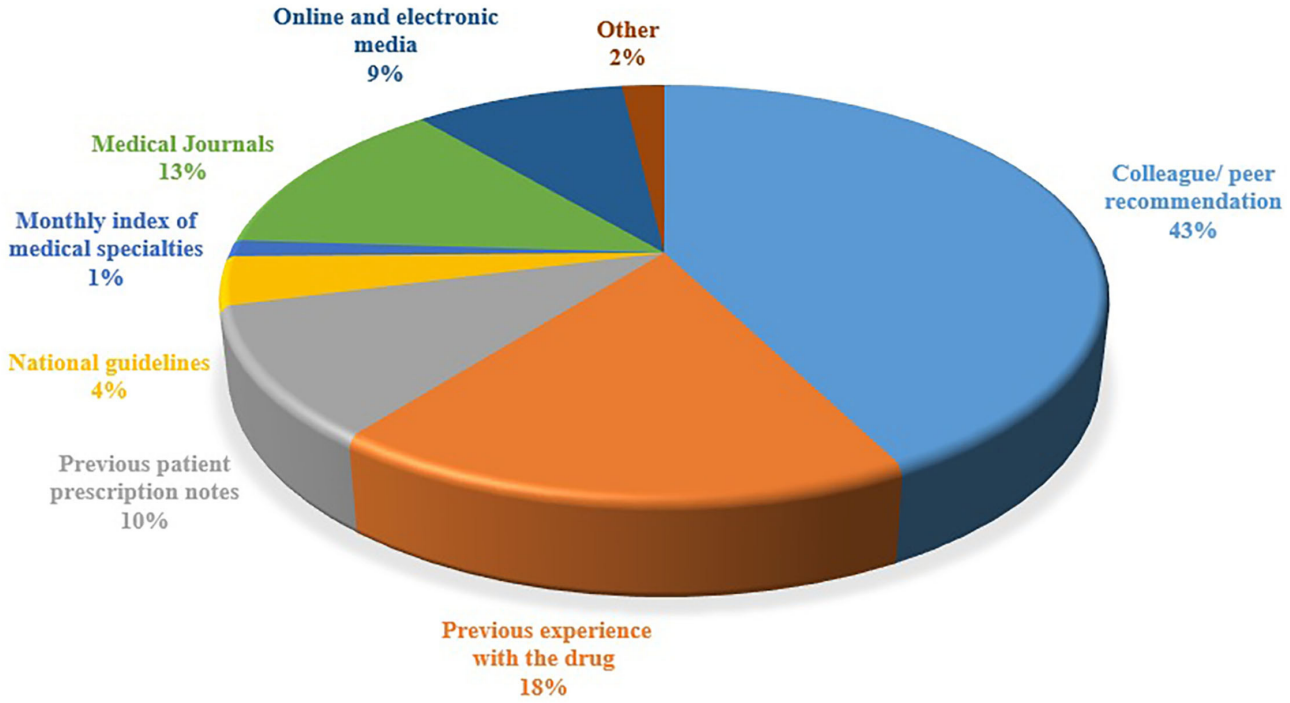

FIGURE 5 | Respondents' major sources of information.

citrate in unexplained infertility to encourage the growth of multiple follicles ($n = 66$; 43.4%), metformin to improve cycle regularity in women with PCOS ($n = 59$; 38.8%) and letrozole to induce ovulation ($n = 31$; 20.4%). Clomiphene citrate has both estrogenic and antiestrogenic characteristics and is frequently used off-label for the treatment of unexplained infertility, both alone and in conjunction with intrauterine insemination (IUI) (20). Femara, or letrozole, was not intended to be a fertility medication. It is, in reality, a breast cancer medication (20). It is, however, increasingly often used off-label to address ovulation problems. According to statistics given at the 34th Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE), a multinational, cross-sectional online survey indicated that 75.5% of physicians suggested OLMU of androgens or letrozole to infertile women (21). Nearly half of fertility experts who did not suggest androgens cited a lack of scientific evidence as to the reason for their therapeutic decision (21). Metformin is one of the most often utilized off-label drugs for PCOS causing infertility issues. Metformin has quickly move up from its early rational use for the treatment of ovulation induction in PCOS to one of the most sought drugs for the condition's management (22). Regardless of the vast number of complete investigations, there is great disagreement among experts with little definitive data on its usefulness in PCOS (23). In our study, we found a similar trend of increased off-label prescribing of both clomiphene and metformin for various reproductive therapies.

According to the current findings, respondents knew that practice of OLMU may compromise safety of patient in certain clinical situations where a progressive risk-benefit ratio isn't completely well-recognized. Around 70% of the respondents showed their concerns when prescribing OLMU about its safety and efficacy in the treatment of FRHIs and consider that some OLMU could increase the likelihood of ADRs. Similar trend was observed in other studies revealing the concern of healthcare professionals toward the safety and efficacy issues of OLMU (16, 24, 25). There is not any clear description of the right to prescribe OLMU anywhere in the globe. The Drugs and Healthcare Products Regulatory Agency in the United Kingdom allows physicians, dentists, pharmacists and independent nurses to prescribe OLMU (26). In Pakistan only physicians have prescription rights and by constraining the prescribing practice of OLMU by the physicians we can prevent the misuse of OLMU. Healthcare professionals are legally restricted to inform patients toward the jeopardies involved in using OLMU (24, 25). The element the there is a lack of data available for using the OLMU must be reflected as a likelihood of hazards to the patient. The physicians should observe legitimate practices that expect them "to obtain informed consent from a person before performing a test or stating a treatment—particularly a treatment that involves some uncertainty". In the present study, the majority of the respondents (75.6%) deemed that the healthcare professionals risk legal liability if they use OLMU in patient care, especially if the patient develops an ADR. Patients, particularly females in less developed nations, face challenges such as a lack of knowledge and information on different health issues, period poverty or stigma, a lack of access to treatments, and gender inequities (1). It is anticipated that healthcare professionals should inform

patients regarding OLMU, however this doesn't appear to be the situation in the present study. It was worrying that around 40% of the respondents informed their patients when prescribing an OLMU whereas more than 75% did not request informed, written / verbal consent from patient or attendant before OLMU. Shakeel et al. reported that the majority of the responders did not notify the patient while prescribing an off-label (27). Varying approaches for informed consent have been proposed in Australia based on different degrees of evidence in off-label medication (28).

In the current study, it was reported by the majority of the respondents (62.5%) that they do not follow any guidelines or regulations for OLMU in their working hospital; however, the response was varied significantly with the working organization (CI 2.14–2.93; $p = 0.037$) and practice area (CI 2.85–4.32; $p = 0.0001$) of respondents. Another study reported that the respondents (74 %) stated that OLMU is not permitted by law, and they (88%) also deemed that there should be clear norms and procedures for OLMU (3). A lack of clear guidelines can lead to uncertainty in physicians' practices and patient discontent. Only by instituting clear norms, direction, and access to scientific knowledge could uncertainty and confusion be avoided (29). The hospital's pharmacy and therapeutics (P&T) committee should be viewed as the arbitrator of institutional policy regarding OLMU, and its decisions should be driven by scientific evidence. When considering OLMU, supporting safety and data must be thoroughly assessed, and a risk-benefit analysis must be undertaken, especially when FDA-approved alternatives are available. Before permitting OLMU therapy, a systematic approach for evaluating scientific evidence should be implemented (30).

The respondents in the present study reported ectopic pregnancy, OHSS and having multiples as the major ADRs of fertility drugs and stated that they do not know how to cope with those side effects. The drugs used to treat fertility issues have their own set of negative consequences (31). Although many of these side effects are harmless and self-limiting, others, particularly those related to gonadotropins, may be severe. Clomiphene has been associated with hot flushes, multiple gestations, visual difficulties, abnormal cervical mucus, and luteal phase deficit (32). OHSS is described by enlarged ovaries and fluid buildup in the abdomen following gonadotropin stimulation and ovulation. A moderate form could occurs in 10–20% of cycles, causing some pain however typically resolving quickly and without consequences (33). Having a trustworthy source of health information is critical for developing a solid theoretical foundation, especially in light of the current internet and social media revolution, which raises numerous concerns about the public's health (34). Colleague/ peer recommendation, previous experience with the drug and medical journals were the respondents' major sources of information for fertility treatment in the present study. Similar outcomes were reported by another study depicting peer recommendations as the major source of health information and prescribing practice (34).

Hence the present study found that respondents were well-familiar with the practice of OLMU in the treatment of FRHIs; yet, they expressed their concern toward decreasing such practice. The findings of our study are supplemented by one more study from Pakistan that shows a comparable pattern of increasing OLMU prescribing trends in clinical settings (16). OLMU is a global thought-provoking problem that has not been explored earlier in Pakistan. Appropriate policies tailored to the local context must be developed and implemented by health establishments to evade the problems associated with inapt prescribing in patients.

The strength of the study lies with the fact that as far as we possibly know there is no such investigation on OLMU focusing particularly on FRHIs reported earlier in Pakistan. This was the first study that was conducted in Pakistan to evaluate the practice of gynecologists/obstetricians in this context. The limitation of this study is the small sample size and the study was conducted with gynecologists/obstetricians in only few clinics and hospitals of single city Karachi; hence the findings are not generalizable to gynecologists/obstetricians in all cities of Pakistan and other countries. Besides, due to the nature of the current study, we were only able to explore the topic superficially, and additional in-depth research, such as investigating off-label practice throughout the country and strategies for overcoming hurdles, might be beneficial in the future.

IMPACT ON PRACTICE

- Further extensive training of health care professionals on off-label issues; for instance, the collective utilization of contemporary sources of information, coupled with informal specialized networks is desired.
- There is a need of improved dissemination of evidences for off-label indications among healthcare team.
- It ought to be pursued that health experts should inform patients regarding OLMU, however this doesn't appear to be the situation in current practice.

CONCLUSIONS

The present outcomes revealed that the practice of OLMU in the treatment of FRHIs was well-observed in the study. However, the respondents were concerned about decreasing such practices by being involved in collective decision-making procedures, and were inclined to accept initiatives aimed at ensuring drug safety in patients. Policies should be established tailored to the local context to analyze OLMU that negotiates patient safety or signifies an improvident medication use.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study was conducted as per the recommendations of the Declaration of Helsinki and the approval was obtained

from the Ethical Review Committee of Sohail University with protocol # 000125/21. The written consent was obtained from the respondents before the study and the goals of the study were explained to them. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SSh, WI, AQ, SN, FB, SSi, HR, and AR made substantial contributions to the conception and design of the study and the analysis and interpretation of the data. SSh and AR made substantial contributions to the analysis and interpretation of the data. All authors drafted the work or revised it critically for important intellectual content, reviewed, critiqued, and approved the final version submitted for publication.

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Injustices in Black Maternal Health: A Call for Different Research Questions, Orientations, and Methodologies

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For decades, Black mothers have been most likely to suffer the worst outcomes of pregnancy, including death. Even though traditional individual level risk factors do not explain racial inequities in maternal morbidity, most studies identify Black race as a predictor, instead of the ways in which our society is structured around racism that makes Black mothers vulnerable to adverse health outcomes. As an example, the U.S is exceptional in incarcerating its residents, and Black men are six times and Black women are three times more likely than their white counterparts to be incarcerated. Relatedly, violent death caused by homicides disproportionately impacts Black communities, such that is the leading cause of death for males and females aged 10–34 years. Estimates suggest that more than 50% of urban residents know more than 10 murder victims, and approximately 200 people are affected by each neighborhood murder. Recent research has begun to shed light on the impacts of stressful neighborhood social conditions on risk of the adverse birth outcomes among Black mothers however, few studies have quantified the impact of macro-social neighborhood factors like violent death exposures and mass incarceration on Black maternal health. Future research that leverages relevant theoretical frameworks, is co-created and co-led with affected communities, and focuses on relevant neighborhood level traumas is warranted if we are to address the longstanding racial inequities in maternal health.

Keywords: Black women, maternal health, mass incarceration, violent death, epidemiology, community-based participatory action research

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INTRODUCTION

"If you are silent about your pain, they'll kill you and say you enjoyed it." -Zora Neale Hurston (1).

If maternal mortality is the tip of the iceberg then maternal morbidity is the base (2, 3). We can understand maternal health as a continuum, with optimal pregnancy outcomes for the mother on one end of the spectrum, and maternal mortality on the other (4, 5). Over the past several decades, maternal mortality has increased nearly two-fold (3), and the rising prevalence of chronic conditions (including obesity, hypertension, and diabetes) as well as cesarean births are likely contributing causes (6). For instance, pregnancy can worsen pre-existing conditions and increase risk for pregnancy complications such as preeclampsia, severe maternal morbidities like heart attack, and the worse outcome of pregnancy- maternal death (7). Pregnancy normally

causes increased cardiac output, heart rate, and blood volume, all of which can cause cardiac strain (8). Cardiovascular disease is now the leading cause of maternal mortality (9), and mothers who endure and survive complications of pregnancy, like preeclampsia, have increased risk of long-term metabolic and cardiovascular disease (10–13).

RACIAL INEQUITIES

Black people are at least 3 times more likely to die from pregnancy related causes than white people, across all age groups (14). From epidemiologic studies we know that Black mothers are also more likely than white mothers to have maternal morbidities, irrespective of the varied definition of "morbidity" across studies (9). Black people are disproportionately burdened by cardiovascular disease risk factors and myocardial infarction during pregnancy, (15) as well as more severe peripartum cardiomyopathy disease (at diagnosis and unfortunately even 6 and 12 months post-diagnosis) (16). Data from the Nationwide Inpatient Sample suggests that Black women are also disproportionately burdened by cerebrovascular events in the peripartum period (17, 18), as well as severe pulmonary complications (19). From 1997 to 2014, severe maternal morbidity increased by 179% in Black women compared to 163% in white women (20). Further, Black women have higher rates of hospital readmission (21, 22), pregnancy associated hospitalization (23), and emergency department visits during the 90 days after delivery (24). Notably, studies have consistently identified racial inequities in maternal mortality across racial groups, after accounting for biomedical, sociodemographic, and behavioral factors (25, 26). The racial inequities in maternal health have been sufficiently documented in analyses comparing Black to other populations. Going forward, novel within-group analyses (comparing Black people to Black people) (27, 28) to identify policy and intervention relevant structural determinants of poor health (29) as well as intervening pathways and protective factors within the groups that have been made vulnerable to race, class, and gender oppression are warranted.

THE SOCIAL CONTEXT AS AN OVERLOOKED DETERMINANT

Social context, which can be understood as the social and political drivers of hierarchies and social stratification, including but not limited to policies and macroeconomic factors (30), has not been the focus of the majority of extant research on racial inequities in maternal health. Unjust exposure to health-harming macro-social factors are likely important drivers of the disproportionate burden of poor health in Black communities (31, 32). Research on determinants of poor maternal health across racialized groups overwhelmingly focuses on individual-level comorbidities (33). Few existing studies examine or acknowledge the relationship between racial inequities in maternal health and structural racism, which includes the social policies, institutional practices, cultural depictions, and other norms that reinforce, uphold, and perpetuate racial inequities (34). This is an important gap in the literature on this topic, especially given evidence that Black people have lower prevalence of five of the common high-risk pregnancy complications, yet have between 2.4–3.3 times higher likelihood of death due to these complications, compared to white people (19).

UNJUST EXPOSURE TO MASS INCARCERATION

Social determinants that are a function of racism and specifically and unequally burden Black people have not been examined as risk factors of poor maternal outcomes using within group analyses. For instance, exposures to "mass incarceration," which refers to the extreme historical and contemporary levels of incarceration, occurrences that are so concentrated in communities of color that it becomes a common stage of in life-course (35). Approximately 50% of Black women have an imprisoned relative, compared to only 12% of their white counterparts (36). Further, Black people are more likely than the overall population to know an incarcerated individual, and to have a neighbor or an intimate partner incarcerated (36). Women make up 83% of those responsible for the costs associated with family member's court costs, which results in a financial burden that compounds any existing struggles to meet basic material needs (37). Direct and indirect contact with the criminal justice system exposes millions of Black women to health harming stressors that threaten their health and that of their families. Recent work suggests that women with experiences of incarceration are more likely to suffer premature mortality than those never incarcerated (38). Further, women (but not men) who have an incarcerated relative have been shown to have higher risk of obesity, heart attack, stroke, and fair or poor health, than those who do not (39). Despite specific calls for research on the life-course influences of mass incarceration on the health of Black people and communities (40), few studies have quantified the direct or contextual effect of mass incarceration on poor health and mortality within this group (41), and none have examined its effect on Black maternal health. This distinct over-exposure to incarceration that Black communities experience may be an important contributor to maternal health inequities and research and action to address this crisis is needed (36, 41).

UNJUST EXPOSURE TO FAMILY AND COMMUNITY VIOLENT DEATHS

More than seven people suffer a violent death every hour, in the United States (42). Homicides disproportionately affect Black populations, such that they are the leading cause of death for Black males and females aged 10–34 (43, 44). Research using a community survey found that over half of urban respondents knew more than 10 murder victims, and approximately 200 people are affected by each neighborhood murder (45). While studies have examined the impact of neighborhood crime on adverse birth outcomes (45, 46), none have examined the unique contribution of neighborhood violent death exposures

on Black maternal health. One study examined the relationship between neighborhood crime and hypertensive disorders of pregnancy using electronic health records linked to police-reported crime incidents, and found null results, likely due to exposure measurement error (47). Indeed, stress from losing a family or community member to violence may negatively impact health promoting behaviors, and poverty and racism likely exacerbate these associations (48). Community, (including state-sanctioned) violence is a public health issue that unjustly affects Black women, who are victims, witnesses, and grieving wives, girlfriends, and mothers of homicide victims. Even when Black people do not experience losing a close relative to violent death, which is rare in many urban areas, the hypervigilance caused by the constant threat of violence negatively impacts the quality of life, mental, and physical health of these people.

HISTORICAL AND CONTEMPORARY REDLINING AS A ROOT CAUSE OF TOXIC STRESS

Residence in disadvantaged neighborhoods is a psychological and physiological stressor (49–51), because neighborhood exposures like social disorder, defined as "visible cues indicating a lack of order and social control" (51), are stress-inducing. Indeed, stressors originating from the neighborhood context are an important contributor to total stress load (52). The "broken windows" theory of urban decline suggests that public disorder causes urban decay and serious crime, and is predictive of poor mental and physical health (53). Black women are more likely to live in disadvantaged neighborhoods throughout their life-course (54), and to experience various family traumas (55). Our understanding of whether and how neighborhoods matter for health has been constrained because much of the literature uses sociodemographic variables from administrative data sources (like from U.S. Census), which may not equal the true neighborhood construct of interest (for example neighborhood disorder or community social ties) (56). Further, there is wide variability in the neighborhood measures used across studies, as is the level of aggregation (census tract, zip codes, block groups, etc.) which makes it difficult to identify what specific neighborhoods characteristics (and at what scale) should be the focus of interventions (56). Unfortunately, we have limited existing data on the predictive ability of structural racism, as manifested by community-level mass incarceration and the community trauma of violent deaths on Black maternal health (26). Nuanced and multi-level quantitative and qualitative (57) evidence on the associations between various manifestations of structural racism on Black maternal health will make it possible to target interventions and policy initiatives at critical periods of exposure across the life-course.

THEORY CAN HELP US ASK DIFFERENT RESEARCH QUESTIONS AND FIND THE RIGHT SOLUTIONS

Reproductive Justice (RJ), conceptualized by Women of African Descent for Reproductive Justice in 1994, is a concept that can be understood as the merging together of reproductive rights and social justice (58). RJ is defined as the interconnected human rights to: (1) have children under the circumstances of one's choosing, (2) not have children, and (3) parent children in safe and healthy communities that are free from individual and state violence (58). Intersectionality, coined by Kimberle' Crenshaw, offers a framework for understanding the unique intersection of racial and gender oppressions experienced by Black women (59). RJ praxis elaborates how activism around bodily autonomy and intersectionality are connected, and facilitates status quo disruption. RJ articulates that the ability of people to determine their own reproductive destiny is directly influenced by the conditions of their community (60). RJ focuses on organizing women, girls, and their communities to resist structural power inequalities through a complete and transformative process of empowerment, one that improves lives of women, ensures healthy families, and sustainable communities (60). Ecosocial theory of disease distribution (61, 62), suggests that: (1) inequitable racial hierarchies prioritize groups who claim superiority at the expense of those deemed inferior; (2) race is reified as biology to establish racial categories; and (3) *inequitable living and working environments* facilitate the biological expression of racism and produce racial inequities in health through embodiment (61, 63–65). The ecosocial approach is guided by the question "who and what drives current and changing patterns of social inequalities in health" (62). The principal focus of this theory is how individuals biologically express exposures occurring from societal and ecological contexts. These frameworks have rarely been integrated to understand the linkages between community trauma and the disproportionate burden of adverse maternal health among Black people, but they can help us understand and most importantly intervene on these multi-level, macro-social determinants and move us toward maternal health equity.

DISCUSSION

Community-based participatory research (CBPR) projects are a critical approach for research on the social-structural determinants of health inequity, and are a crucial part of dismantling oppressive structures (66–68). CBPR projects that focus on associations between macro-social exposures including (but not limited to) community trauma caused by mass incarceration and violent deaths and maternal health of Black people (using within group analyses) are urgently needed. The COVID-19 pandemic, which highlighted and exacerbated longstanding racial inequities in health and resource distribution, should make it clear why research on racialized communities that is not grounded in relevant theories and does not center the lived experience and various ways of knowing of affected communities in the conception, design, implementation, and dissemination stages will cause more harm than good. Given this, research that is focused on the liberation of oppressed communities, and is led by members of affected communities (as equal thought leaders) should be prioritized for funding by local and national funders and philanthropic organizations. This perspective calls for different research questions- ones that are not bound by

the current available data, are not based solely the intellectual curiosity of researchers, are informed by relevant theories and frameworks, and use participatory research methodologies *for action*.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SS-J conceived of, wrote, and edited the manuscript.

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Latina Women in Academia: Challenges and Opportunities

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Latina women and other ethnic and racial groups continue to be underrepresented in science, technology, engineering, and mathematics (STEM) fields, including public health. This underrepresentation of people from diverse backgrounds and lived experiences in academic public health and other scientific disciplines is a form of epistemic oppression, exclusion that hinders contribution to knowledge production and advancement. Our analysis of 2021 data from the Association of Schools and Programs of Public Health indicates that Latinos/as represented only 6.0% of all instructional faculty and 6.1% of all tenured faculty at schools and programs of public health. We discuss the ways in which sociopolitical contexts, family-level dynamics and gendered norms, and institutional contexts hamper Latinas' full participation in academia. We propose solutions such as redefining metrics for success, leadership accountability, equity analyses, cluster hiring initiatives, and instituting structured mentoring and leadership programs. Bold actions are needed if we are to advance the scientific enterprise and address the diversity and equity problem in public health.

Keywords: Latinas in higher education, public health, racism, academia, oppressed group

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INTRODUCTION

Despite the goal of the field of public health to promote the health of the public and to address health disparities and its commitment to social justice, certain ethnic and racial groups continue to be under-represented (UR) among the faculty of schools and programs of public health (1–3). For these reasons, Ramirez-Valles (4) asserted that the field of public health continues to struggle with an equity problem. Moreover, the under-representation of people from diverse backgrounds and lived experiences in academic public health and other scientific disciplines is a form of epistemic oppression, defined as systematic exclusion that hinders contribution to knowledge production and advancement (5). We concur with scholars who cogently argue that epistemic oppression limits and creates inherent flaws in scientific research (6). Further, the intersection of gender and ethnicity create additional barriers, such that women of color are particularly under-represented especially in academic and administrative senior positions, and face multiple challenges in academic career progression (2, 7, 8).

Several excellent reviews revealed the critical gaps that remain in advancing women in the sciences, including public health (1, 2, 9–11). This perspective article is not based on an extensive

review of relevant literature on this topic. Instead, we target key articles for discussion and build on the existing body of work. In addition, we write this perspective from our own lived experience as first generation scholars (offspring of parents who did not earn a college degree), first or second generation immigrants, and as the first or only Latina women in our respective departments and schools, at one point or another in our careers. By centering this review on our lived experience, we hope to highlight how the struggles women faculty of color often experience are rooted in structural, systemic conditions.

We begin by providing a brief overview of trends on Latinas in academia, discuss the ways in which racism and a variety of other structural determinants limit the representation of Latinas and other groups in academia, and propose solutions to address the diversity problem in academic public health by highlighting the importance of resources, initiatives and mentoring that make a difference for Latinas and other women of color in the academy to be seen, affirm their voice, and advance their careers (3, 4, 12).

NATIONAL TRENDS ON LATINA REPRESENTATION IN ACADEMIA

Data from the National Center for Education statistics demonstrate the significant shortage of Latinas in higher education. Among full-time instructional faculty employed in degree-granting postsecondary institutions in 2019 (most recent data available) women represented 47.2% of all faculty (n = 398,165), increasing from 31.8% in 1991 (n = 165,213). In contrast, in 1991, Latinas represented <1% of all full-time faculty (0.78%, n = 4,069) rising only to 2.6% (n = 21,814) in 2019.

A study by Goodman et al. (1) demonstrates that these striking disparities are also evident in academic public health. Specially, the authors found that from 1997 to 2017, individuals of Latino/Hispanic origin increased by 2% at schools of public health and represented 8.5% of all primary instructional faculty at schools and programs of public health.

For the present article, we retrieved 2021 data from the Association of Schools and Programs of Public Health online data center, and found that Latinos/as (n = 330) represented only 6.0% of all instructional faculty (n = 5,485) and 6.1% (n = 149) of all tenured faculty (n = 2,453) at schools and programs of public health in the United States (49 of these are at the University of Puerto Rico Graduate School of Public Health). Although these percentages are small, tenured Latinos constitute a larger proportion than Black faculty, who only represent 4.3% of all tenured faculty. Underrepresentation of Black faculty merits a thoughtful critical discussion that is beyond the scope of this perspective piece (13). We also found a huge gender gap across ranks when comparing Latino/a men and women. At the Assistant Professor level, Latinas (n = 82) far outnumber Latino men (n = 36), representing 69.5% of Hispanic faculty at this rank. This advantage continues at the Associate Professor level, with 62.3% of Latinas holding this rank compared to 37.7% of Latino men. However, at the full Professor rank, this trend inverts between Latina women and men (44.3% vs. 55.7%, respectively).

STRUCTURAL CONTEXTS

In the following sections, we focus on sociopolitical contexts, family-level dynamics and gendered norms, and institutional contexts that hamper Latinas' full participation in academia.

Sociopolitical Context

The immigration climate of the nation has a profound effect on Latino scholarship. In recent years, we have seen a retrenchment of inclusive immigration policies and increased criminalization of immigrants (14). From 2008 to 2013, the Secure Communities program grew from 14 jurisdictions in the US to all 50 states (plus the District of Columbia) and allowed the sharing of law enforcement information with federal immigration enforcement authorities. During the 2000's, annual immigration to the US fell by almost half to about 600,000 people per year, a level not seen since the 1980's (15). Some of the authors of this manuscript have direct experiences with parents or close family members who have been undocumented or continue to live through this reality. Indeed, these experiences have been the impetus behind some of our careers, but they also exert personal tolls with practical consequences for advancing our research. Recruiting Latino/a participants for research studies, for example, under this political climate requires a substantial investment of time, trust building, and connecting with organizations that can serve as brokers and allies for our research. This additional level of investment is often not borne by our non-Latino colleagues. Moreover, current US immigration policy has been crafted to source the labor needs of the American economy producing a highly bifurcated system of geography and education, at times favoring some groups while dehumanizing others (16). Thus, the social capital needed to maneuver through the appointment, tenure and promotion process can uncover and deal with traumatic processes of oppression and marginalization that our families and communities have experienced. Examples of programs designed to build social capital include (among others) New Connections and Health Equity Scholars for Action, which link new Latina and other underrepresented scholars and investigators with established researchers, who themselves may have successfully dealt with issues of oppression (17). Lastly, while we are heartened to see that some universities have put policies in place for faculty to document research challenges related to the COVID-19 pandemic, it is not clear if similar processes have been instituted to account for the racial reckoning the nation has recently undergone, including the very visible anti-Black and anti-immigrant policies and practices that shape American life.

Family-Level Dynamics and Gendered Norms

Families and caregiving responsibilities are not inherent barriers to success in academia. However, they produce differential outcomes across gender when norms and expectations by those in academic institutions stem from the assumption that all faculty

have substantial spousal support in the form of a stay-at-home partner (18). Stay-at-home support in the form of a spouse has historically been perceived to be an advantage in academia since it allows for intensive work schedules that maximize the kind of scholarly output that is most revered (e.g., publications, grants). However, about 90% of the spouses of women in academia work outside the home full time, in contrast to 50% of their male counterparts (18). Single women in the academy may be able to adhere to this intense work schedule at first glance, but they also report having less work balance than their married colleagues (19). Although Latinas report more work balance than Latinos (19), there is a dearth of research documenting Latinas caregiving responsibilities such as aging parents or disabled family members. Moreover, regardless of marital status, women in academia who wish to have their own biological children must contend with the inherent conflict between building their careers in the early stages at the same time in which they may need to make crucial family and reproductive decisions (20). Further, Latina faculty also cite the added burden caused by the "push and pull" of their roles as exemplars and mentors to students of color while simultaneously feeling the pressures of their roles as mothers and spouses (21). A study of highly-ranked science programs revealed that female faculty have fewer children than their male colleagues, and nearly twice as many female faculty as men reported having fewer children than they desired because they pursued a science career (22). Career-building and family tensions may be particularly problematic for women pursuing academic careers in global public health, given the need to spend considerable time abroad (7). These conflicts are exacerbated whether or not parental roles are achieved biologically given the lack of integration between family and work in the academy. Indeed, work/family balance is commonly cited as a barrier to academic success among faculty of color (23), and family pressure is still one of the top reasons cited by women exiting tenure track positions in academia (18).

Institutional Contexts

Discrimination and Bias

Structural contexts also include institutionalized racism, bias and discriminatory practices. In their review of gender and ethnicity in 15 leading social science and public health universities, Khan et al. (2) identified broad structural factors that create barriers to diversity in schools of public health. Importantly, they found that gender and ethnicity interact, creating obstacles especially for women of color as they attempt to climb academic ranks. Their analysis revealed that the proportion of ethnic minority women declined from mid- to senior-level academic ranks in all 15 of the universities that they examined. They concluded that marginalization, prejudice and discrimination against ethnic minority women account for these findings. These are manifested, for example, in lower pay for similar positions, temporary contracts, and other practices that lead to lower chances of recruitment and promotion for ethnic minority women.

Other structural factors are at play affecting women's scientific pursuits. For example, there is a lack of representation of women on NIH review panels, and funding gaps. Shen (24) reported that over a period of approximately a decade, a Freedom of Information Act request from *Nature* revealed that the percentage of women on NIH review panels barely shifted from 25% in 2003 to 30% in 2012. Interestingly, these figures mirror approximately the percentage of women applying for and receiving grants during that period. There are also funding gaps, such that in 2012, the NIH awarded 30,768 to men and 13,025 grants to women. Moreover, the average amount of the award was higher for men ($507,279) than for women ($421,385) (24).

There is also evidence that different standards are applied to scholarship dealing with diversity-related topics. For example, one analysis revealed bias against manuscripts dealing with diversity topics such that in early rounds of the review process, diversity manuscripts relative to non-diversity papers were 12 times more likely to be rejected than accepted (25). Moreover, using an experimental design, editorial board members who were asked to review abstracts of manuscripts showed evidence of applying "stricter standards" when evaluating diversity papers, such that quality of manuscripts was associated with editorial decisions for diversity papers but not for other topics (25). Given the importance of publications in obtaining academic positions and achieving tenure and promotion, Latinas and other scholars engaged in social justice and diversity-related research may be subject to biased review of their work, putting their academic opportunities and career progression at risk.

Diversity Climate

A "critical mass" of groups that have been historically underrepresented in academia can support a climate of diversity and inclusion. The relatively small numbers of African American, Latino/a, and Native American students and faculty in institutions of higher education may contribute to the perception that they do not "belong." Several studies document the importance of sense of belonging in academic settings (11, 26, 27). Because of their profound social significance, race or ethnicity contribute to self-efficacy, learning experiences, and choices. Due to racism and other psychosocial processes in the social environment, race/ethnicity is differentially related to a variety of "opportunity structures," including exposure to role models and mentors that can facilitate (or limit) skills and outcome beliefs [(28), p. 103].

A sense of belonging and self-efficacy also must be studied in the contexts of successes and failures. Many programs encouraging academic achievement among UR groups tend to focus on the pathways and processes of success. Rarely do they discuss the recovery from failures or setbacks. Yet, in academic settings, achievement often is met with setbacks along the path to success. Some examples of setbacks include rejection of a scientific manuscript submitted for publication, an unsuccessful attempt at promotion, a mediocre or unsatisfactory annual performance review, and a poorly-scored grant application. In academic institutions with few students and faculty of color, setbacks or failures may be magnified for UR groups. These magnification effects occur both within UR individuals (i.e., how they perceive themselves) and how others may perceive them. Moreover, given the competitive nature of

academia, Latinas and other UR faculty members may not receive guidance and strategies for overcoming these setbacks. Because of their greater presence on campus, those in majority groups who experience a failure may not perceive the event as indication that they do not belong. Similarly, the tendency to value what is familiar may lead to unconscious or conscious "cloning" practices, defined as the tendency of faculty to almost always hire "a clone" of themselves, by powerful institutional committees that make hiring and promotion decisions (29). For example, search committee members may discount or devalue the work or educational credentials of UR job candidates whose academic background and research experiences may differ from their own. "Cloning" can also operate among review, promotion, and tenure committees that are charged with evaluating the performance and career trajectories of UR faculty.

Inequitable Academic Practices and Norms

Latinas and other UR faculty members may also be subjected to inequitable service obligations and value conflicts. "Cultural taxation," the expectation that UR faculty members carry out a variety of diversity service and teaching activities, presents a potential impediment to success (30). Faculty of color often have to teach diversity-related courses, participate in faculty recruitment activities, donate their time and effort to diversity-related training, give guest lectures on diversity-related topics, represent their programs or departments at meetings requiring diversity-related input, serve on search committees requiring minority representation, and so on. Additionally, UR faculty often are made to feel that declining to take on these tasks would undermine the diversity efforts of the University (31). Thus, cultural taxation could adversely affect effort spent on the metrics for success that are more valuable in academic advancement, such as publications and grant-funded research (30).

Moreover, Latinas may experience value conflicts with fundamental norms in academic settings. Self-promotion is central to recognition and advancement in many universities. Members of cultural groups who look down upon self-aggrandizement, however, find it difficult to engage in what is perceived to be "obnoxious self-promotion" activities that are essential to highlight their research, scholarship, and other academic accomplishments (29). UR faculty members also may experience challenges carrying out other normative academic behaviors, such as networking in an unwelcoming environment. Furthermore, UR faculty may not have had similar socialization experiences during their training (access to mentors or extensive networks) that lead to successful integration in the academic profession (31).

DISCUSSION AND SOLUTIONS

We end this article by proposing solutions that address the systemic, structural reforms needed to advance the career paths of Latinas and other underrepresented scholars.

Leadership Accountability. All of the factors described above present challenges for recruitment, retention, and advancement of Latinas and other UR groups in public health. Institutions cannot address diversity if they do not acknowledge the problem. It is incumbent on the leaders of organizations and institutions of higher education to invest in diversity. Investment includes both financial and social resources. Schools and programs also should be held accountable for analyzing the diversity of their faculty both in hiring, retention, and promotion. There is a need for bold policies that are supported, monitored and enforced by institutional leaders.

Redefine Metrics of Success. It is critically important to specify outcomes and indices of how "success" will be defined and measured. This is especially important for UR faculty who engage in diversity-related and community-engaged research. Moreover, institutions should establish systems for tracking retention and advancement. We agree with other scholars who have recommended that institutions should publicly report gender and ethnicity of faculty, including at different seniority levels, and that these data be used for rankings and accreditation [e.g., (2, 4, 9)].

Pay and Service Equity Analyses. Institutions, schools and programs should also engage in periodic pay and equity analyses. Tracking of service obligations should include consideration of "invisible" service, such as informal mentoring to students of color to whom the faculty member is not assigned as the advisor of record, or for additional labor provided to students of color in the form of counseling, training and referrals for academic support.

Cluster-hiring, in which three or more individuals are hired simultaneously, is another strategy to recruit and retain faculty of color. Cluster hiring eliminates the risk of isolation in departments where the faculty member of color is the "only one." These circumstances are known to breed feelings of isolation–both social and intellectual–which can lead to professional stagnation or departure from academia (23). Indeed, some programs (e.g., NIH's FIRST) have been launched specifically for the purpose of creating cohorts and communities of underrepresented scientists who are committed to diversity and inclusive excellence. Furthermore, institutions should develop and maintain pipeline programs that include graduate students and postdocs who could transition into early career academic positions with appropriate support.

Structured mentoring programs and leadership programs for women can provide needed resources and guidance to UR faculty members. UR mentors who have strategically overcome some of the institutional and other barriers described in the sections above may be particularly well-suited to advise UR students and junior faculty on methods for dealing with these circumstances (32). Race/ethnic-concordant faculty mentors might also serve as important role models that promote UR students' and junior faculty members' perceptions that they, too, can succeed in academic settings. Of course, the lack of established UR researchers who can serve as mentors can become a self-perpetuating cycle (23), underscoring the need to assure that institutional policies, practices and structures contribute to the success of Latinas and other groups in academic settings. Lastly, private foundations and the National

Institutes of Health [e.g., (33, 34)] have developed programs to support faculty of color and these programs should be adopted by institutions and offered to faculty, especially early stage scholars.

Taken together, our findings and existing research on women of color in public health highlight the need to end epistemic oppression for all groups, including Latinas. We are encouraged by the growing recognition that structural racism, which includes anti-immigrant policies, permeates all of the work we do in public health. Bold actions are needed if we are to advance the scientific enterprise and address the diversity and equity problem in public health.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Available only *via* the Association of Schools and Programs of Public Health. Requests to access these datasets should be directed to data@aspph.org.

AUTHOR CONTRIBUTIONS

AA-L, SE, and KF contributed to the writing of the manuscript and ideas for sections of the manuscript. SE and AA-L conducted the analyses. SM-G reviewed the existing literature, the findings, and contributed significantly to ideas for the manuscript. All authors contributed to the article and approved the submitted version.

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Exploring Extension Agent Capacity and Readiness to Adopt Policy, Systems and Environmental Change Approaches

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Introduction: Enhanced Extension outreach strategies combine traditional direct education programs with public health approaches like policy, systems, and environmental (PSE) change. However, the Cooperative Extension system and county-based Family and Consumer Sciences (FCS) Extension agents have historically prioritized direct education programming and diffusion of enhanced outreach strategies has varied. Extension personnel may lack capacity and readiness for successful PSE change implementation. This study explored perceived acceptability, capacity, and readiness for PSE change work among FCS Extension agents in two states.

Method: A survey was developed framed by selected domains from the Consolidated Framework for Implementation Research: Intervention Characteristics, Inner Setting, Characteristics of Individuals, and Process. All questions utilized a 5-point Likert scale, except for an item examining respondents' stage of change regarding PSE change strategies. Descriptive statistics and response frequencies for all variables were calculated.

Results: Survey responses (n = 116) indicated PSE change work was perceived as valuable. Potential barriers included perceived complexity, organizational readiness issues (e.g., reporting and evaluation structures; performance incentives), and worries about stakeholder responses in shifting away from direct education. Responses indicated self-efficacy for skills important in implementing PSE change. Most respondents (53%) indicated being at the pre-contemplation or contemplation stage of change in pursuing PSE change work.

Discussion: Combining PSE change strategies and direct education programming allows Extension to do what it does best – provide effective programs to improve and sustain health and wellbeing of individuals and families. Findings are informative for others aiming to build capacity within community educators, Extension and public health professionals to implement PSE change.

Keywords: PSE, Cooperative Extension, public health, PSE change, family and consumer sciences, Consolidated Framework for Implementation Research, health education, PSE barriers

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INTRODUCTION

The Cooperative Extension System (Extension) is a nationwide network providing community-based, nonformal education through local Extension offices affiliated with states' land grant universities. Extension has sought to improve quality of life and wellbeing for individuals and communities for more than 100 years by extending research findings from the university to communities through a partnership between federal, state, and local governments (1). While Extension's mission has been characterized as "Taking the University to the People" (2), a top-down paradigm, local Extension efforts take a grassroots approach characterized by county-based Extension agents working in partnership with residents and other stakeholders to solve problems. With offices in or near most U.S. counties, the footprint of county Extension offices and personnel differs by state (3). The Extension model and nationwide infrastructure have been envied by the healthcare sector, inspiring transformational ideas to increase healthcare access both parallel to and in collaboration with local Extension offices (1, 4, 5).

Agriculture, youth development, community development, and family and consumer sciences have been the primary focus for Extension education efforts. Campus-based, subject-matter Extension specialists train and support county-level educators known in some states as Extension agents. Local Extension agents identify and address community needs through education and outreach typically delivered through direct education and demonstrations (6). However, in the last decade Extension has increasingly focused on spurring long-term, sustainable changes requiring diverse partnerships, coalitions, and enhanced collaboration.

Family and Consumer Sciences (FCS) programs focus on enhancing community resilience and improving quality of individual and family life. In most states, FCS Extension addresses nutrition and food safety, human development, financial management, and health content areas. FCS Extension agents are skilled users of direct education methods reflecting Extension's traditional, expert-model for program delivery (7). Direct education methods usually address the individual or interpersonal/family level of the social ecological model and aim to increase knowledge and change behaviors (8). An enhanced approach combines both direct education and public health approaches like policy, systems, and environmental (PSE) change strategies. PSE change strategies extend benefits beyond individuals and families attending educational programs to communities, producing long-term, sustainable community health improvements (9).

Direct education and PSE change are more effective when implemented together (10). Enhanced approaches leveraging FCS direct education and public health strategies enable impacts at multiple social ecological model levels, including social networks, living and working conditions, and political factors determining individual health behaviors and community health outcomes (11). For example, PSE change strategies can include price change (e.g., improving pricing of healthier food items over less healthy items), space redesign, altering social norms, community empowerment, and redistributing resources (12). Enhancing healthier lifestyle supports for all community members can help alleviate some structural and social determinants of health known to exacerbate health inequities (12–14).

Supplemental Nutrition Assistance Program Education (SNAP-Ed) and other federally funded initiatives, such as the Centers for Disease Control and Prevention (CDC) High Obesity Program (HOP), have largely driven the increased emphasis on PSE change strategies in Extension. SNAP-Ed-funded Extension programs were mandated to provide comprehensive nutrition education programs including PSE change interventions starting in 2010. Extension PSE change approaches implemented through SNAP-Ed have evolved to address social determinants of health by promoting policy, systems and environmental changes impacting places where people live, work, and play (13, 15). In 2014 through HOP, CDC began funding Extension work specifically to address PSEs in counties with adult obesity rates over 40% (16). Additional Extension efforts to integrate PSE change with direct education include the Well Connected Communities Initiative, a partnership between the Cooperative Extension System and National 4-H Council funded by Robert Wood Johnson Foundation. The initiative supports systems change to advance health equity and improve social determinants of health (17).

The shift to PSE change work from primarily delivering direct education has challenged some county-based Extension personnel and state-level specialists, particularly those with a longer tenure within the traditional Extension system (18). Although Extension has been engaged in PSE change work more than 10 years, exploration of perceived acceptability among Extension professionals charged with implementation has been limited primarily to SNAP-Ed and other special grant-funded projects. For example, capacity limits noted among Extension and non-Extension SNAP-Ed implementers in one state included limited knowledge, training, resources, and experience with PSE change approaches (19). Others reported multi-level barriers to PSE change implementation, including lack of readiness among SNAP-Ed partner sites and implementers, and prioritizing direct education over PSE change work (20). Extension professionals' beliefs about the role of Extension may also pose challenges to PSE implementation (21). Participants in one national survey included Extension FCS, 4-H, nutrition education, and community development professionals; responses indicated varying levels of willingness to apply PSE change approaches in youth development activities. Most thought PSE change work would be a "big shift" in their work (22). Aside from this youth development focused survey, effort to understand agent viewpoints broadly within an Extension system has been limited.

The increased public and private investment into Extension to influence health-promoting PSE change and advance health equity make understanding perceptions and attitudes of FCS Extension agents critical. To better understand attitudes, perceptions, and readiness to implement PSE change strategies, we conducted a survey of FCS Extension agents in two neighboring states with similar trajectories for introducing PSE change into Extension work, including CDC's High

Obesity Program (HOP) funding and SNAP-Ed PSE change implementation. This study explored perceived acceptability of PSE change work among FCS Extension agents in two states and broadly examined potential barriers and facilitators to advancing Extension's PSE change work.

METHOD

Sample

FCS Extension agents in Kentucky and Tennessee were invited to participate in an online survey in Spring 2020. Kentucky and Tennessee are neighboring states with similar obesity-related disease burdens, each comprised of primarily rural counties with few large metropolitan areas; both have county-based FCS Extension agents. Existing email listservs and distribution lists for each state were used for recruitment. Inclusion criterion was currently serving as an FCS Extension agent in Kentucky or Tennessee. Selection of a position title other than FCS Extension agent terminated the survey. There were no exclusions based on gender, race, or ethnicity.

Survey Measures

We developed our survey by using selected domains and constructs of the Consolidated Framework for Implementation Research (CFIR) (23). The CFIR was developed based on review and synthesis of published implementation theories and provides a list of constructs within general domains thought to influence implementation. The CFIR, however, does not specify interaction between constructs and allows researchers to choose those most relevant for the study setting. The CFIR was selected because it can be used to guide formative evaluations and is well-suited for measuring complex, multi-level influences on implementation in real-world settings.

The CFIR includes 37 constructs in five domains: intervention characteristics, outer setting, inner setting, characteristics of individuals involved, and the process of implementation. As advised by CFIR developers, the research team reviewed CFIR domains and constructs, identified those of interest, and selected constructs most relevant for the study purpose and context (23) (see **Table 1**).

Research team members independently drafted questions in a shared document to address selected domains and related constructs, then jointly reviewed questions to clarify wording. After revision, the team reviewed the questions again by domain and construct to determine those most relevant and suitable given the survey purpose and sample. After this review, wording of survey questions was further refined. Questions and aligning domains/constructs were reviewed by a panel of FCS Extension agents and Extension specialists with PSE change experience and experts from the public health sector with knowledge of PSE change implementation and evaluation. All feedback was combined, and the survey was further refined by the research team based on suggested edits and reviewer comments. Questions utilized a 5-point Likert scale with response options from "strongly disagree" to "strongly agree" with a neutral midpoint ("neither agree nor disagree") except for one item examining respondents' stage of change for PSE change implementation.

TABLE 1 | Selected domains and constructs - consolidated framework for implementation research (23).

CFIR Domain	Selected Constructs
Intervention Characteristics *Characteristics of the intervention being implemented into a particular organization*	• Intervention source • Relative advantage • Adaptability • Trialability • Complexity
Outer Setting *The economic, political, and social context within which an organization resides*	• Patient (clientele) needs & resources • Peer pressure • External policies and incentives
Inner Setting *Structural, political, cultural, and organizational contexts through which the implementation process will proceed*	• Structural characteristics • Networks and communications • Culture • Implementation Climate - Tension for change - Learning climate • Readiness for Implementation - Available resources
Characteristics of Individuals *Characteristics of individuals involved with the intervention and/or implementation process, including cultural, organizational, professional, and individual mindsets, norms, interests, and affiliations*	• Access to information and knowledge • Knowledge and beliefs • Self-efficacy • Individual stage of change • Individual identification with organization
Process of Implementation *Interrelated series of sub-processes that may not occur sequentially*	• Planning • Executing • Reflecting and evaluating • Engaging

Data Collection

Kentucky utilized the Qualtrics platform (Qualtrics.com); Tennessee used QuestionPro (questionpro.com). Both systems included an embedded document describing PSE change within the Extension context for review prior to completing the survey. Survey items were the same across both states. The survey invitation included a brief description of the survey, an attachment defining PSE change strategies within Extension contexts, and an embedded survey link. A reminder email was sent to non-respondents 1 week after the initial invitation. A subsequent final reminder email was sent 1 week later. FCS Extension agents were encouraged to participate regardless of exposure to or experience with PSE change work. Completion of the survey was considered consent to participate. Responses were anonymous; no incentives were offered. The Institutional Review Boards at the University of Kentucky and the University of Tennessee approved the study protocol.

Data Analysis

Data from each state were cleaned and combined for analysis. Strongly agree and agree responses were collapsed to form a single category, as were strongly disagree and disagree responses (24, 25), resulting in three response categories: agree, neutral,

and disagree. Variables were collapsed due to scarcity of data within the strongly agree and strongly disagree categories. Descriptive statistics and response frequencies for all variables were calculated. Surveys were analyzed using Microsoft Excel (version Microsoft 365).

RESULTS

Participant Characteristics

A total of 116 FCS Extension agents completed the survey between Kentucky ($n = 43$) and Tennessee ($n = 73$). The sample was predominantly White, with a Master's degree or higher, mirroring the overall makeup of FCS Extension agents in both states. The largest percentage of participants had an educational background in Family and Consumer Sciences studies. Age and tenure with Extension was evenly distributed across both states (**Table 2**). The response rate for Tennessee and Kentucky, respectively, was 67.5 and 45.7%.

TABLE 2 | Participant demographic characteristics ($n = 116$).

Characteristics	Kentucky ($n = 43$)	Tennessee ($n = 73$)	Total ($N = 116$)
Age, *n* (%)			
20–39	14 (33%)	35 (48%)	49 (42%)
40–59	21 (49%)	29 (40%)	50 (43%)
60–69	8 (19%)	9 (12%)	17 (15%)
Race			
Black /African American	1 (2%)	5 (7%)	6 (5%)
White	41 (95%)	64 (90%)	105 (92%)
Two or more mixed race/other	1 (2%)	2 (3%)	3 (3%)
Education			
Bachelor's degree	5 (12%)	24 (33%)	29 (25%)
Master's Degree or higher	38 (88%)	49 (67%)	87 (75%)
Current role			
County Director and / or Agent (FCS – 100% adult)	40 (93%)	51 (70%)	91 (78%)
County Director and / or Agent (FCS/4-H – split assignment)	1 (2%)	18 (25%)	19 (16%)
Other	2 (5%)	4 (5%)	6 (5%)
Educational background			
Child and family studies	10 (23%)	19 (26%)	29 (25%)
Food and nutrition	14 (33%)	21 (29%)	35 (30%)
Family and consumer sciences	19 (44%)	31 (42%)	50 (43%)
Health	1 (2%)	8 (11%)	9 (8%)
Other	-	3 (4%)	3 (3%)
Extension employment, years			
<5 years	5 (12%)	27 (37%)	32 (28%)
5–15 years	18 (42%)	18 (25%)	36 (31%)
15–25 years	10 (23%)	14 (19%)	24 (21%)
≥25 years	10 (23%)	14 (19%)	24 (21%)
County of work			
Rural	36 (84%)	59 (81%)	95 (82%)
Urban	7 (16%)	14 (19%)	21 (18%)

Intervention Characteristics

Overall, responses indicated FCS Extension agents perceived PSE change work as valuable. Analyses showed high levels of agreement for survey items related to perceived value of PSE change for community health (83%) and intervention source, adaptability, and relative advantage (see **Figure 1**, Intervention Characteristics). Lack of clear guidance and plans, and difficulty reporting outcomes, contributed to perceptions of perceived complexity of PSE change work, a potential barrier. Fewer agreed (21%) PSE change strategies are too complicated to seriously consider for their counties, but more than one-third were neutral.

Inner Setting

Survey items addressing the CFIR domain inner setting had lower agreement and higher neutrality (response of "neither agree nor disagree") than other domains, particularly for readiness and structural characteristics (see **Figure 2**, Inner Setting). For example, 45% of respondents agreed Extension is committed to addressing PSE changes for the long term, while 45% were neutral.

Implementation climate, a construct of the inner setting domain, generated incongruent responses. Respondents largely agreed Extension needs to include PSE change efforts for local success (77%) and Extension administration recognizes PSE change work as important (77%). However, only 34% agreed PSE change efforts are rewarded within Extension; 40% were neutral. Responses for learning climate items, an implementation climate sub-construct, indicated 62% of respondents are willing to shift from direct education to allow for PSE change work, but 66% have fears about negative consequences for changes in program outputs (direct contacts) likely resulting from such a shift. Similarly, responses for networks and communication items, an inner setting construct, indicated a majority (60%) have difficulty determining how to prioritize PSE change opportunities over other activities; 57% worried about stakeholder responses if some programs are limited or discontinued to allow for PSE change work (see **Figure 2**, Inner Setting).

A majority (69%) agreed the Extension organizational culture was supportive of PSE change work; fewer (61%) agreed the respondent's county office culture was supportive. Responses were nearly evenly divided regarding recognition and value of PSE change work in the Extension performance evaluation structure: 35% agreed PSE change work was valued and recognized, 32% disagreed, and 33% were neutral (see **Figure 2**).

Characteristics of Individuals

Overall, most respondents have self-efficacy for skills important in implementing PSE change work: engaging with non-traditional partners (81%), leading a group in planning and prioritizing strategies (63%), and persuading others to buy in

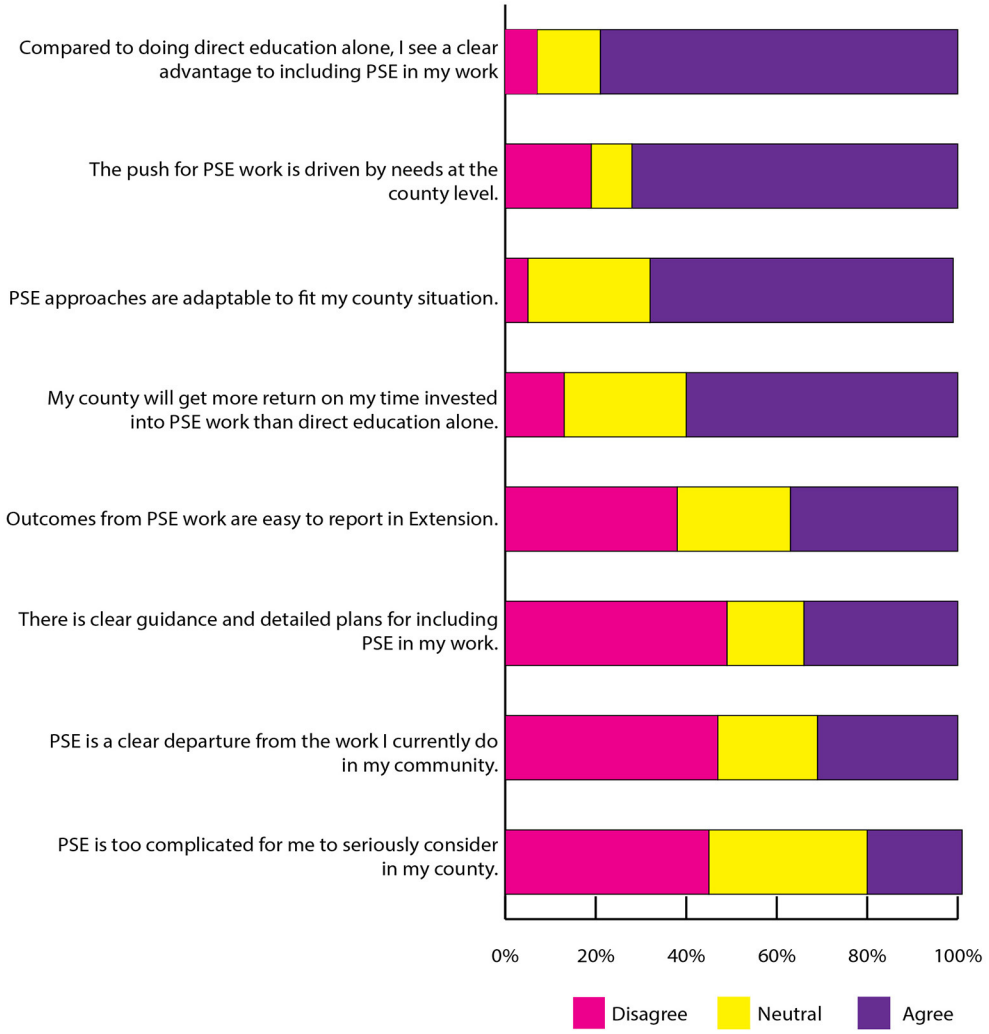

FIGURE 1 | Intervention characteristics.

(57%) (see **Figure 3**). A majority (88%) agreed PSE change can make a difference in their communities, but lower agreement existed for other survey items addressing the knowledge and beliefs construct of the characteristics of individuals domain. For example, only 41% of respondents felt competent in doing PSE change work; 31% said PSE change is outside their comfort zone. Responses to these questions also had a higher neutrality compared to others in the same domain. Most respondents (53%) indicated being at the pre-contemplation or contemplation stage of change in pursuing PSE change work in their counties; few indicated action (22%) or maintenance (9%) stages.

Process

Survey responses for process domain items were conflicting. Despite a minority (18%) indicating awareness of how PSE change efforts are evaluated, 58% said they can effectively share PSE-related successes in their communities. Only 27% agreed with the statement, "I see myself as a champion for PSE change in my community." Nearly half (48%) indicated neutrality.

DISCUSSION

Extension has historically worked at the community level to speed adoption of innovations, like PSE changes, by working through Extension agents and with local coalitions and partners. The Extension System and has more than a decade of experience diffusing PSE change strategies (10, 26). The CDC-funded HOP is limited to a small number of qualifying counties, yet successfully implemented PSE change strategies from HOP have diffused across counties. Until now, FCS Extension agent capacity to conduct PSE change work was largely assumed without investigating acceptability and readiness to include PSE change approaches in county programming. Study findings provide insights into FCS Extension agent readiness to implement PSE

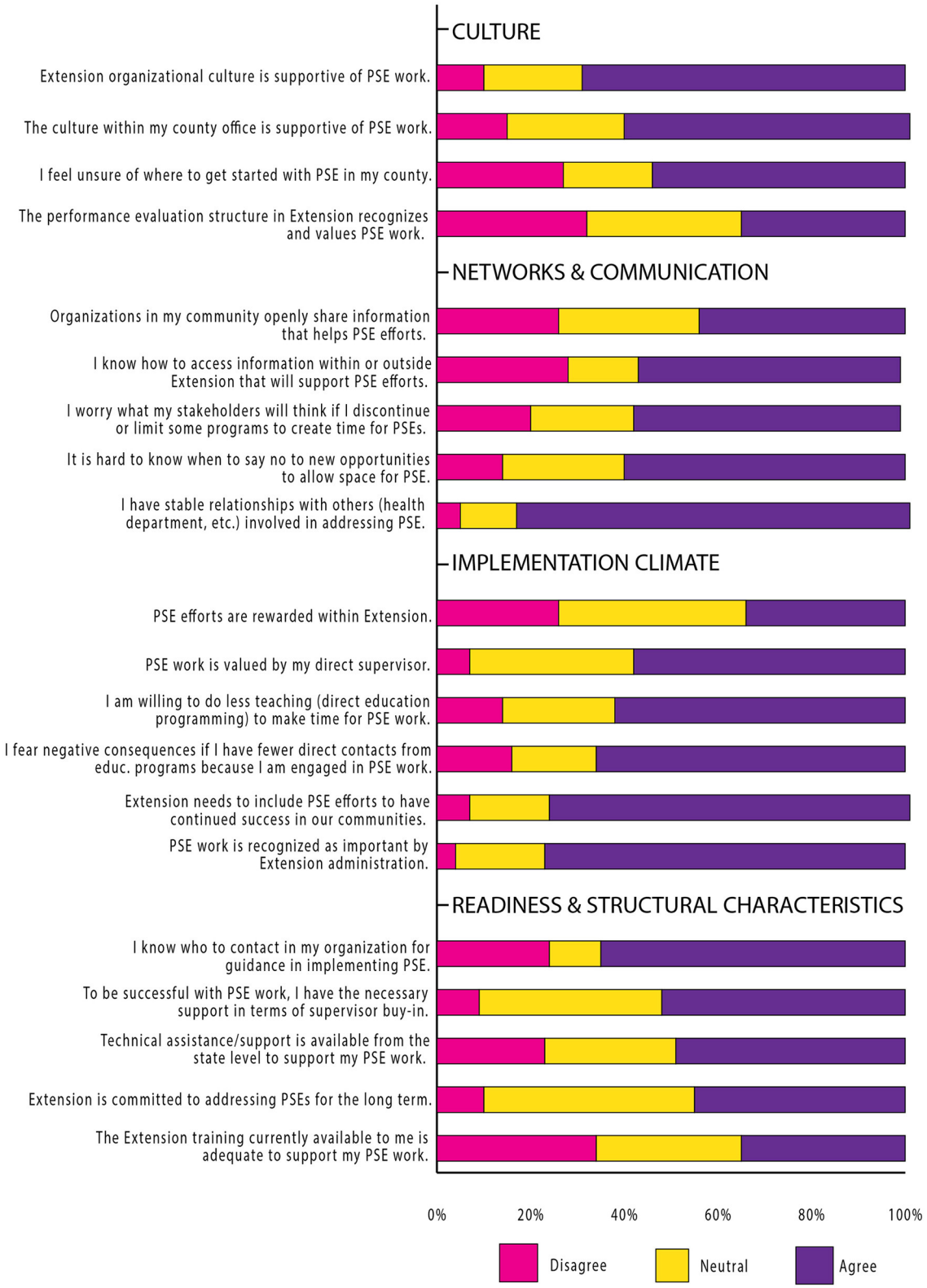

FIGURE 2 | Inner setting.

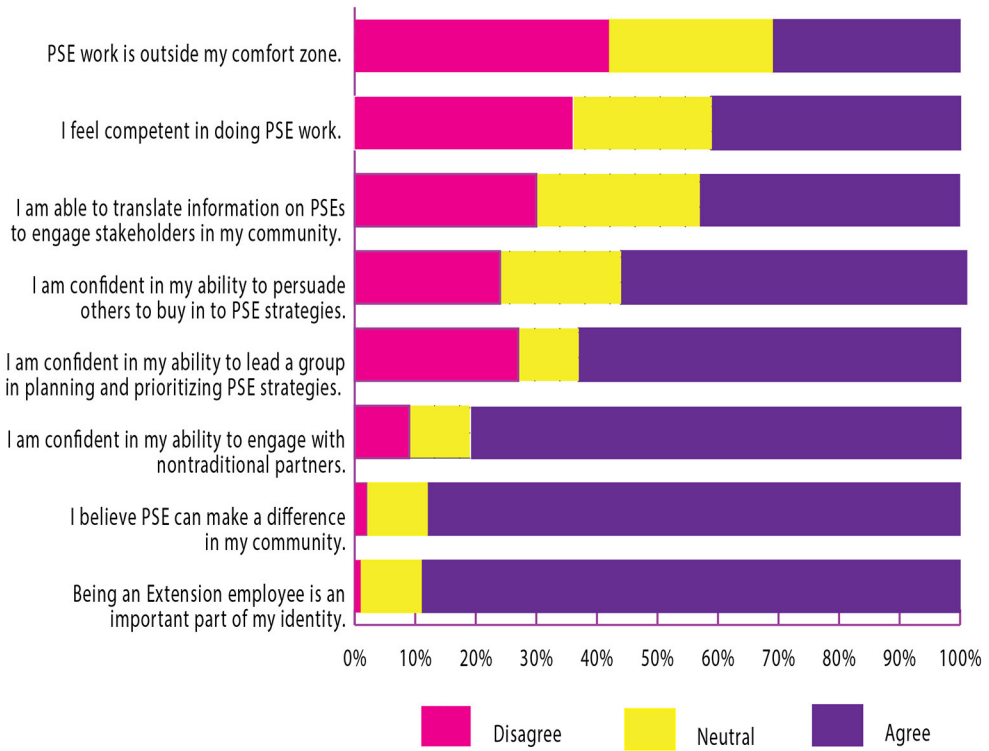

FIGURE 3 | Characteristics of individuals.

change work and highlights barriers to adoption of PSE change strategies identified by respondents.

Overall, participants perceived organizational (Extension) support for PSE change approaches but also conveyed doubts about Extension's long-term commitment. This finding is consistent with results reported in a national survey of Extension professionals – 38% felt PSE change was a fad, potentially reflecting broader sentiments about Extension's involvement in community change work (22). Uncertainty regarding Extension's long-term commitment to PSE change work could be driven by continued reliance on grant funding (e.g., SNAP-Ed and CDC) and slow pace of organizational change, particularly within reporting and evaluation structures valuing direct education over sustained change through implementation of PSE change strategies (20).

Extension Agent Readiness

Extension agents are instrumental facilitators of county-level PSE change work (27–29) but come to Extension with varying academic backgrounds and experiences typically excluding public health (30). FCS Extension agents traditionally prioritize direct education programming addressing nutrition, health, and wellbeing. Similar prioritization of direct education has been noted among SNAP-Ed implementers specifically tasked with supporting PSE strategies (20). Skills for effective educational program delivery differ from the skills, support, and resources required for successful PSE change strategy implementation. PSE change work is valued within the national Extension system (29, 31) but implementation varies between counties and states likely due to knowledge and skill gaps among county-based Extension agents.

Agreement for relative advantage, relative priority, and adaptability suggest FCS Extension agents believe PSE change work is important for community change and valuable for Extension (32). However, high neutrality in several CFIR domains may indicate gaps in basic understanding of PSE change noted in other surveys of Extension professionals (33). PSE change work is inherently more complex than direct education methods. Training needs in PSE change terminology, concepts, implementation, and evaluation have been noted for SNAP-Ed and EFNEP professionals and others implementing PSE change (20, 33–35). In this study, 35% neutrality on the question, "PSE change work is too complicated for me to seriously consider in my county" suggests some had not pondered PSE change implementation. Neutral and agree responses combined (56%) nearly match the 53% indicating being at pre-contemplation or contemplation stages in pursing PSE change work in their counties.

Findings regarding PSE change evaluation were incongruent. A majority (58%) agreed they can effectively share successes related to PSE change in their communities, but only 37% agreed PSE change outcomes are easy to report. Notably, fewer than one in five participants were aware of how PSE change efforts are evaluated. Other surveys of Extension professionals involved in

PSE change work revealed uncertainty about what qualifies as a PSE change strategy and inability to identify PSE change efforts in their communities (33). Gaps in knowledge of evaluation methods, reporting, and sharing successes suggest additional training and resource needs for evaluation, a finding consistent with other studies (36).

Organizational Barriers

Despite high levels of agreement that the Extension organizational culture is supportive of PSE change work, survey findings suggest notable internal barriers limiting adoption. These barriers illuminate opportunities to support county-level PSE change adoption, like streamlining outcome reporting and increasing training, support, and technical assistance for implementation and evaluation.

Complexity and perceived relative priority within the organization are barriers to PSE change implementation (32). Worries about negative consequences from fewer direct contacts and lower levels of agreement regarding internal recognition for PSE change work may reflect perceptions that direct education is valued over PSE change the organizational level. Most participants had difficulty declining direct education opportunities to allow space for PSE change work. In many states, including those in this study, Extension agents have high levels of autonomy in choosing programmatic focus in their communities. Local demand for Extension programs typically exceeds capacity. The array of programmatic options available to Extension agents may be overwhelming (37). These contextual factors may contribute to FCS Extension agents' challenges in prioritizing PSE change work.

Additional barriers included worries about stakeholder perceptions with modifications to plans of work, fewer direct education activities to increase PSE change efforts, and performance evaluation structures not recognizing or valuing PSE change work. Despite system-level efforts to value outcomes over number of people reached, direct contacts remain a metric of success. Fears of negative consequences from program changes resulting in fewer direct contacts may limit adoption. Inaccurately perceived negative consequences for reduced contacts resulting from PSE change work, compared to direct education, can be corrected through clear communication from upper administration and those performing personnel evaluations (38).

Expectations for implementing multi-level approaches should be included in job descriptions and clarified in scope of responsibility for current employees (39). Two questions in the characteristics of individuals domain regarding identification with the organization ("Being an Extension employee is an important part of my identity") and knowledge and beliefs ("PSE change can make a difference in my community") garnered the highest levels of agreement on the survey. Because direct education is traditionally preferred and prioritized, Extension professionals may also prize their teaching role and claim this as part of their identify, causing potential conflict with expectations for PSE change work despite recognizing value in these approaches. Cognitive dissonance between the direct educator and PSE implementer role may be remedied by presenting a "program plus PSE" approach, where traditional educational programs are enhanced with PSE change interventions. Emphasizing advantages of PSE change over direct education alone while also acknowledging complexity may help personnel feel more confident and enhance compatibility of PSE change alongside the educator role (18, 32). Support for collaborative, multi-level approaches is essential to motivate personnel to tackle complex community-level issues.

Organizational Readiness

SNAP-Ed and EFNEP professionals have been the focus of several published studies about readiness for PSE change within Extension, an understandable focus given federal mandates to incorporate PSE change with direct education (19, 34, 40, 41). An unintended consequence, however, may be views among Extension agents erroneously limiting scope of PSE change efforts to SNAP-Ed and EFNEP eligible sites and participants. Opportunities to engage in PSE change work exist across all program areas within Extension. The need for non-SNAP-Ed partners has been documented (40). Adequately addressing social determinants of health and health equity within communities requires new approaches to translate and demonstrate PSE change in settings unaffiliated with nutrition education programs. Similarly, strategies aimed beyond increased access to healthy foods and physical activity, the primary focus thus far, must be demonstrated (14).

In the past, PSE change work absent an intentional focus on equity perpetuated health disparities in communities (often predominantly Black, Indigenous, and People of Color) made vulnerable by historical, ongoing economic disinvestment, social exclusion, and systemic oppression. Deliberate action by Extension personnel to address structural and social determinants of health, like racism and power, must be included in any PSE change work. In 2021, Extension published a new National Framework for Health Equity and Wellbeing (Framework) identifying and outlining health equity, social determinants of health, and community engagement as core themes in a national approach to health programming (31). The new Framework offers an opportunity to support state and local personnel in aligning PSE change work with established metrics of health equity (42–44).

In Extension, PSE change is often touted as a valuable approach to changing contexts that shape health outcomes, rather than affecting individual behavior through education alone. However, Extension is not immediately equipped to address PSE change failures leading to health inequities (45–47). The relative racial, ethnic, and gender homogeneity of Extension personnel represented in this study sample mirror personnel found at most 1862-designated land grant universities. Personal and individual biases, coupled with organizational and institutional racism and power differentials, require significant investment in organizational and individual capacity building for Extension staff at all levels if PSE change work is to address health equity and not cause further harms. As capacity or readiness improves, frameworks, such as R4P, Bounded Justice, or Collective Healing, can guide community-led PSE change processes toward health equity (45, 48, 49).

These findings are informative for entities working with Extension to implement PSE change strategies and highlight important considerations for rolling out large initiatives and working with diverse communities. Extension personnel have varying degrees of readiness to engage in PSE change work shaped by organizational and community factors, personal attitudes and biases, and educational/professional backgrounds. An organizational pivot to prioritize PSE change and a significant influx of resources (funding, training/education, partnerships) is needed for broad implementation within the national Extension system. Partner organization personnel should critically examine assumptions about individual and organizational readiness and seek to understand attitudes and perceived barriers of Extension personnel within community contexts.

Limitations

This study has several limitations. First, the survey has not been validated for assessing beliefs and perceptions regarding PSE change work; however, using a validated framework and constructs for survey development was intentional for reducing bias. Second, our sample size was relatively small and the response rate may have been impacted by the onset of the COVID-19 pandemic during spring 2020. Thus, we cannot generalize findings and are unable to assess the potential differences among FCS Extension agents, for example, by years of experience. Third, data were collected from FCS Extension agents irrespective of previous knowledge or experience about PSE change. While this was intentional to fully understand baseline knowledge and perceptions, the high degree of neutrality in responses may result from questions not being applicable to all respondents. Because survey content related to job duties, respondents may have perceived some responses to be more acceptable than others, introducing social desirability bias.

CONCLUSION

PSE change implementation may appear daunting as a new endeavor for FCS Extension agents. However, the outcomes of equitably implemented PSE change strategies are beneficial for health promotion and are worth pursuing. Combining PSE change work with traditional Extension direct education programming allows Extension to do what it does best—provide research-based, effective programs and interventions to improve and sustain the health and wellbeing of individuals and families. Integrating PSE change within Extension aligns our work with the growing body of evidence showing PSE changes lead to sustained positive health outcomes, providing a novel mechanism for Extension to partner with public health entities for improved community health. Our findings provide unique insight informative for other Extension and public health entities looking to build capacity within community-level educators, Extension personnel, and public health professionals to implement PSE change work. Moving forward, Extension should ensure PSE change strategies are presented as a priority to all staff within the organization.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was reviewed and approved by University of Tennessee Institutional Review Board and University of Kentucky Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LW, HN-B, NJ, and LK jointly developed survey instrument and study design. LW, HN-B, and NJ coordinated data collection and contributed to data interpretation. SJ conducted data analysis. LW led manuscript development. All authors contributed to read and approved the final manuscript.

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Validity Evaluation of the College Student Physical Literacy Questionnaire

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Background: Physical literacy (PL) is an important tool to promote physical activity of individuals, and the level of physical literacy of individuals affects their physical activity behaviors. Currently, the physical fitness of college students in China is a prominent issue, and assessing physical literacy among college students may provide tools and directions to further promote physical fitness and precisely intervene in physical activity behaviors of college students in the future. This study aimed to develop a college student physical literacy questionnaire (CSPLQ) to address the lack of currently available physical literacy assessment tools for Chinese college students. We hoped to collect validity evidence of this questionnaire to measure the validity of the physical literacy self-assessment questionnaire among Chinese university students.

Methods: An initial pool of items was obtained from existing research instruments, literature, and expert advice. An expert review panel evaluated its content. A subsequent validation process reduced the pool of items. We conducted a validation factor analysis of the CSPLQ using structural equation modeling. The relationship between physical literacy and other variables was also examined using correlation analysis.

Results: The item content validity index (ICVI) of CSPLQ was 0.70–0.95. The CSPLQ was composed of a total of 38 items across 3 domains (physical and behavioral domain, affective domain, and cognitive domain) and 7 dimensions (motor skills, motor skills, physical activity, perceptions of healthy living, perceptions of physical activity, motivation to engage in physical activity, and confidence to engage in physical activity). The factor validity of the CSPLQ was determined by significant loading of all items on their expected factors, with good data model fit and good stability between two independent samples were demonstrated. Each subscale had a Cronbach α coefficient >0.9 and was strongly correlated with each other. The correlation coefficients between college students' physical literacy and other variables, including athletic ability, physical condition, physical attractiveness, physical fitness, frequency of physical activity, and length of physical activity, all reached a significance level of $P < 0.05$.

Conclusion: The CSPLQ has sufficient evidence of validity. The development of the instrument showed evidence of validity for the content, response process, internal structure, and relationships with other variables.

Keywords: physical literacy, college students, questionnaire, reliability, validity

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INTRODUCTION

Physical literacy (PL) refers to "the motivation, confidence, physical ability, knowledge and understanding to value and actively participate in physical activity (1)." Physical literacy is the ability of an individual to achieve a healthy lifestyle (2), and is very important for the development of an individual's physical and mental health (3). In 2015, the International Physical Literacy Association (IPLA) issued a consensus statement on physical literacy (4), which was supported by more than 1,300 sports organization leaders and experts. The IPLA considers physical literacy to have four interconnected and essential elements: motivation and confidence (emotional domain), physical ability (physical domain), knowledge and understanding (cognitive domain), and behavioral participation in lifelong physical activity (behavioral domain) (4). Individuals with higher levels of physical literacy will be more confident and capable of participating in various physical activities (5), while individuals with lower levels of physical literacy will have less physical activity behaviors (6).

Taking physical literacy as an important means to promote individual physical activity, it is necessary to use physical literacy assessment tools to help understand people's physical literacy level (7). In the past two decades, scholars in different countries have developed some physical literacy assessment tools or assessment models. Such as Canadian Agility and Movement Skill Assessment (CAMSA) (8), physical literacy assessment for youth tools (PLAY) (7), Canadian assessment of physical literac (CAPL) (9), Portuguese Physical Literacy Assessment Questionnaire (15–18 years old), Australia's physical literacy assessment model based on Structure of the observed learning outcome (SOLO) (10). However, because different assessment tools are based on different conceptual models, they are applicable to different ages and populations. For example, the three physical literacy assessment tools in Canada (CAMSA, PLAY, CAPL) and Portugal's (PPLA-Q) are designed according to the stage and continuous characteristics of children and adolescents' growth and development (8, 9, 11). CAPL is suitable for 8–12 years old, PLAY is suitable for 7–12 years old, CAMSA is suitable for 8–12 years old, PPLA-Q is suitable for 15–18 years old. Australia has established an assessment model based on the "SOLO classification theory" to observe the performance results of various elements of physical literacy in specific situations, which can be applied to all groups of people, but there is still no specific quantitative assessment tool. Although some scholars have proposed that developing individual physical literacy in early life is more conducive to participation in sports and physical activities throughout life, the structural model of physical literacy should not be limited to children and early adolescents, and more ages and groups should be explored to achieve People maintain purposeful physical pursuits and activities throughout life (12).

In China, the physical health of students has attracted the attention of the government. According to the latest national student physical fitness test data, college students are the group with the largest number of students in all academic stages whose physical fitness test scores do not meet the national test requirements (13). Under this realistic background, the physical literacy assessment of college students may provide tools and directions for further promoting the physical health of college students and accurately intervening in the physical health of college students in the future. To our knowledge of published articles, there are currently few tools available for assessing physical literacy in college students.

Zhao (14) constructed a structural model of adolescent physical literacy evaluation (14) from four dimensions of sports knowledge, sports habits, sports conditions, and sports spirit. However, this evaluation model is quite different from the IPLA's definition of the conceptual model of physical literacy. Ma et al. (15) used the Perceived Physical Literacy Instrument (PPLI) for validation among Chinese college students (15). Although this study showed that PPLI had better construct validity and reliability in 622 Guangdong college students, whether PPLI adaptation for more Chinese college students remains to be further explored. First of all, the modeling population of PPLI is professional physical education teachers, and its evaluation content is very professional in sports. Secondly, PPLI uses Cantonese, and its language habits are quite different from Mandarin, which is currently mainly used in China. The validation samples used in this study were also from Cantonese-speaking regions. In addition, in the assessment tools of physical literacy of children and adolescents, most motor skills tests are used to reflect the physical ability of individuals, such as PLAY and CAPL. However, some scholars believe that more motor skills tests may not be conducive to large-scale assessment of physical literacy. On this basis, they proposed that the use of self-reported motor skill levels may facilitate the development of large-scale physical literacy assessments (12).

Therefore, in order to meet the needs of large-scale physical literacy assessment of Chinese college students, we aimed to design a preliminary questionnaire to identify the physical literacy of Chinese college students (College student physical literacy questionnaire, CSPLQ). Then collect the validity evidence of the questionnaire to measure its validity in the physical literacy assessment of Chinese college students, so as to objectify and quantify the subjective and qualitative college students' physical literacy.

MATERIALS AND METHODS

Research Process

The research process of the CSPLQ consists of two stages: item generation and validity process (**Figure 1**). Referring to the validity framework recommended by AERA-APA (1999), this study uses content, response process, internal structure, and relations with other variables to measure the validity process of CSPLQ (16, 17).

Item Generation

The research team evaluated existing literature on physical literacy assessments and compared scholars' views on the concept of physical literacy. In the end, we chose Chinese scholar Li et al. to define the concept of "physical literacy" (18). According to her concept, physical literacy is divided into four fields, including emotional field (motivation and confidence),

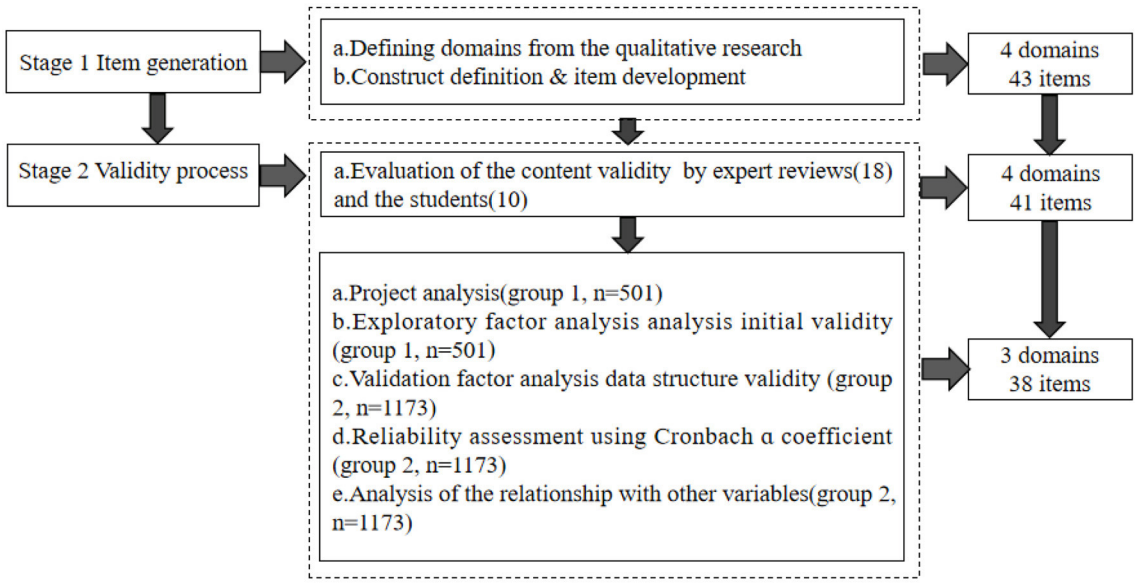

FIGURE 1 | The CSPLQ research process.

physical field (physical ability), cognitive domain (knowledge and understanding), behavior domain (behavior of participation in lifelong physical activity). Entries in each field of inclusion must be persistent and suitable for self-reporting. All secondary and tertiary indicators in the initial indicators were designed with the help of an expert group consisting of three experts and scholars with more than 10 years of experience in sports measurement and evaluation. These items were rated using a five-point Likert scale, with a score of 1 = completely disagree to 5 = completely agree.

Validity Process

To determine the effectiveness of the content, we invited our second panel of experts. This group comes from our literature search from CNKI and obtained 18 Chinese scholars (8 with senior titles, 5 with associate senior titles, 2 associate researchers, and 3 postdoctoral fellows) with relevant research. To align experts with their concepts of content effectiveness metrics (relevance, clarity, comprehensiveness), we explained the definitions of these metrics to experts. Relevance is defined as the ability of design questions to reflect content. Clarity is clarity with regard to wording and description of concepts. Finally, a questionnaire that includes all content areas is defined as comprehensive. We emailed them the original question. The subjects of the questionnaire are divided into objective questions and subjective questions. The objective questions are in the form of a Likert scale, and the evaluation level is "1 = not at all important ∼ 5 very important," and the importance of the first-level indicators, second-level indicators and observation points (third-level indicators) is investigated. The higher the score, the higher the recognition of the reasonableness of the indicator by the surveyed experts. Subjective questions mainly seek experts' suggestions on whether the indicators are reasonable, increase or decrease, and corrections. After gathering expert input, the initial three-person panel revised some questions based on the feedback. The next step was to evaluate the descriptions of the questionnaire with the help of 10 college student volunteers. They completed questionnaires and gave their suggestions for difficulties understanding the descriptions of the questions or answers. We have rephrased the items that needed revision to be grammatically and colloquially acceptable and understandable. We sent the corrected questionnaire back to the second-round panelists, asking them to indicate their level of agreement on the relevance and clarity of each item and the comprehensiveness of the questionnaire. They were asked to rate the clarity and reliability of each item and the comprehensiveness of the questionnaire on a scale from 1 to 5 (1 = completely unreasonable to 5 = very reasonable), collect expert answers, and calculate content validity metrics. At this stage, items were retained if the Item Content Validity Index (ICVI) was ≥0.70 (19), indicating acceptable agreement. The IRA for relevance and clarity of the new questionnaire was estimated using the Scale Content Validity Index (SCVI). To estimate SCVI, we averaged S-CVI/Ave by summarizing ICVI and dividing by the number of items. The comprehensiveness of the questionnaire is described using the total number of experts. This process questionnaire went from 43 items to 41 items. The questionnaire is prepared according to the language habit of Mandarin Chinese and can be completed in 10–15 min. For the assessment of the internal structure, we used data from two questionnaire surveys (groups 1 and 2). For the evaluation of construct validity, two questionnaires (Group 1 and Group 2) were used. Item analysis followed by exploratory factor analysis (EFA) was conducted for Group 1. Item redundancy was determined based on the following assumptions: (a) loading factor > 0.4 for each item, (b) mean inter-item correlation > 0.20, and (c) no overlap or wording redundancy between items

(19). This process turned the questionnaire into 38 items in 3 domains. Questionnaire validation was performed by validated factor analysis (CFA) using Group 2 data to assess dimensions as a measure of the internal structure of the questionnaire (20). The dimensions of the instrument were assessed using selected fit index criteria. The criteria used were: (a) Root mean squared error approximation (RMSEA) < 0.1 (21); (b) p-values should be significant and chi-square divided by degrees of freedom < 3 (22); and (c) Comparative fit index (CFI) > 0.90 (23). After model fitting, the internal consistency of the questionnaire was measured using Cronbach's alpha for the total questionnaire and the three sub-questionnaires (24). The relationship between exercise capacity, physical condition, physical attractiveness, physical fitness, frequency of physical activity and time spent in physical activity was analyzed using correlation analysis. All questionnaires were administered between 15 March 2021 and 10 May 2021. The questionnaire was administered on a 5-point Likert scale, 1 = completely inconsistent to 5 = completely consistent. Statistical analysis of all data was performed using SPSS 22.0 software.

Participant Recruitment

In order to study the content structure of the questionnaire, we conducted two data collections in total. The pre-test survey site is selected in the university town of the researcher's city. The pre-test selected college students from 7 colleges and universities at the 211 level, provincial key, ordinary second, third, and junior college levels. The electronic questionnaires were distributed through the "Mike" questionnaire platform, and a total of 501 valid questionnaires were returned (meeting the requirement of 5–10 times the number of questions). Among them, 238 were boys (47.50%), with an average age of 19.88 $\pm$ 1.21 years. There were 263 girls (52.50%), with an average age of 19.71 $\pm$ 1.13 years. There are 362 (72.26%) college students with rural household registration and 139 (27.74%) urban household registration students. The formal test randomly selected 15 colleges and universities in the eastern, western, southern, northern and central regions of China. For the formal survey, a total of 15 colleges and universities in the eastern, western, southern, northern, and central regions of China were selected for random sampling. A total of 1,217 questionnaires were received, and a total of 1,173 valid questionnaires were received. Among them, there were 533 boys (45.44%), with an average age of 19.98 $\pm$ 1.40 years. There were 640 girls (54.56%), with an average age of 19.09 $\pm$ 1.47 years. There are 911 students with rural household registration (77.66%) and 262 students with urban household registration (22.34%).

RESULTS

Item Generation

Based on the relevant literature on physical literacy assessment and the recommendations of a three-person expert group, we divided college students' physical literacy into four first-level indicators, including emotional, physical, cognitive, and behavioral domains. For these four first-level indicators, we have expanded the second-level and third-level indicators. The first evaluation index system of this study was obtained (**Table 1**).

Validity Process

Expert Review and Response Process

A preliminary questionnaire with 43 questions was designed according to the first version of the questionnaire index system, and then the number of items in the questionnaire was reduced to 41 after validity analysis. Among them, the two observation points of "daily lying time" and "frequency of physical activity in a week" have been deleted, and two observation points have been modified, such as "body shape preference" being changed to "aesthetic preference," and "activity participation" being changed to "activity" appreciation. "The ICVI of the last questionnaire ranged from 0.70 to 0.95. Indicates that the majority of experts agree with the selected item and its related issues. The consistency of the relevance, clarity and comprehensiveness scores of the final 41-item questionnaires were 82.33, 78.99 and 81.02%.

Ten college student volunteers helped evaluate the descriptions of the questionnaire. After evaluation, the description of Q24 "I have mastered the knowledge of sports safety protection" was changed to "I have mastered the knowledge of sports safety protection," and the Q36 "I like watching various sports events" was changed to "I like watching various sports activities very much (competition)."

Internal Structural Analysis

Project Analysis

SPSS 22.0 software was used to analyze the basic characteristics of the measurement items on the 501 survey data in the pre-test. **Table 2** provides the mean, standard deviation, skewness, and kurtosis of the 41 questions answered in the initial questionnaire on physical literacy of college students. From the skewness and kurtosis analysis results of the 41 items, their absolute values are all <2 (19), indicating that the respondents' responses to the items belong to a normal distribution. In order to further analyze the degree of distinction of the items, the survey data were divided into high and low groups of 25% up and down according to the total score of the questionnaire. A t-test was performed on the two groups of data to compare the differences between the high and low groups on each item (19). The analysis results are shown in **Table 2** for the CR values. Except for Q17 which did not reach the significant level of 0.05, the CR values of the remaining 40 questions all reached the significant level of 0.001. Correlation analysis was performed between the scores of each question and the total questionnaire score. The analysis results show that the r value of Q17, Q18, and Q33 questions is lower than 0.2 (20). Therefore, according to the project analysis results, questions Q17, Q18, and Q33 are deleted. There are 38 questions left in the end.

Exploratory Factor Analysis

In order to analyze the structure of CSPLQ, SPSS 17.0 software was used to conduct exploratory factor analysis on 501 pre-tested survey data. The results showed that the Bartlett sphericity test was ∼4,991.83 chi-square, and the KMO value was 0.943, reaching the significant level of 0.001, indicating that the new

TABLE 1 | The first evaluation index system.

First-level indicator	Secondary indicators	Three-level indicator
A1Physical domain	B1 Motor skills	Basic movement skills
		Core stability
		Motor coordination
		Action accuracy
		Hand-eye coordination
	B2 Motion skills	Body rhythm
		Speed quality
		Strength quality
		Endurance quality
		Flexibility
		Agility
		Balance
		Athletic ability
		Motor learning ability
A2Behavioral domain	B3 Physical activity	Daily physical activity
		Moderate-intensity physical activity time per week
		Frequency of physical activity during the week
	B4 Sedentary behavior	Daily screen behavior
		Daily sedentary behavior
		Daily lying time
A3Cognitive domain	B5 Cognition of healthy lifestyle	Daily diet
		Sleep
		Living habit
		Health
	B6 Cognition of physical activity	Physiological responses to exercise
		Physical activity safety
		Physical activity principles
		Principle of sedentary behavior
A4Emotional domain	B7 Motivation to participate in physical activity	Value judgement
		Emotional needs
		Body type needs
		Social needs
		Health needs
		Physical examination needs
		School rules
		Friend influence
		Parents urge
		Interest driven
		Aesthetic preference
		Activity appreciation
	B8 Confidence to participate in physical life	Confidence in bodily functioning
		Confidence in mobility
		Confidence in body shape

questionnaire is suitable for factor analysis. The data in this study were rotated using the maximum variance rotation method (Varimax). Combined with variance contribution rate and gravel plot analysis, seven factors are obtained, and the eigenvalues are all >1. The variance explanation rates of these seven factors after rotation are 16.142, 13.681, 8.049, 7.922, 6.919, 6.199, and 5.793%, respectively. The cumulative variance explained rate after rotation is 64.704%. Since the Q17, Q18, and Q33 questions have been deleted during the project analysis, there are 7 secondary indicators remaining. Therefore, the total number of items in this exploratory factor analysis is 38. The seven factors extracted by factor analysis are consistent with the original dimension concept, and the analysis results are shown in **Table 3**. It can be seen from the table that the factor loadings of all

TABLE 2 | Questions and descriptive statistics of CSPLQ ($N = 501$).

Coding	Project description	*Mean*	*SD*	Skewness	peak	CR	Correlation coefficient with total scale
Q1	I can walk, run, jump, throw, hit, kick, etc.	4.269	0.980	1.999	−1.507	−9.310	0.438**
Q2	I can do a standard plank	3.659	1.119	−0.509	−0.500	−18.583	0.659**
Q3	I am good at coordinated movements	3.633	0.947	0.037	−0.499	−17.257	0.670**
Q4	I can do those movements that require high precision very well	3.232	0.965	−0.300	−0.128	−19.527	0.709**
Q5	I have good hand-eye coordination	3.615	0.877	−0.085	−0.309	−16.193	0.661**
Q6	My body has a better sense of rhythm than my peers	3.244	0.921	−0.140	−0.070	−16.540	0.685**
Q7	I'm noticeably faster than my peers	3.098	0.980	−0.217	−0.082	−16.840	0.664**
Q8	I did better than others in strength tests	3.030	0.911	−0.082	0.084	−16.163	0.640**
Q9	I am good at endurance activities such as cycling, running, swimming, etc.	3.024	1.039	−0.485	0.070	−14.284	0.606**
Q10	I am more flexible than most of my peers	3.020	1.062	−0.573	−0.030	−10.907	0.498**
Q11	I can do activities that require flexibility	3.082	0.955	−0.233	0.044	−15.818	0.658**
Q12	I have good balance	3.357	0.884	0.165	−0.241	−16.141	0.670**
Q13	I'm better at sports than most of my friends	3.128	1.008	−0.395	−0.117	−18.016	0.692**
Q14	Most sports are easy for me	3.192	1.006	−0.326	−0.154	−21.589	0.759**
Q15	I do physical exercise or other physical activity almost every day	3.481	0.939	−0.158	−0.279	−14.750	0.596**
Q16	I do physical activity lasting 30 min or more at least 3 times a week (e.g., cycling, running, playing, etc.)	3.645	1.063	−0.692	−0.337	−15.908	0.570**
Q17	Almost every day I spend a lot of time on my phone or on my computer	2.643	0.933	0.037	0.292	−1.737	0.109*
Q18	I spend most of my waking hours sitting or lying down	2.733	0.968	−0.150	0.211	−2.875	0.152**
Q19	I know the knowledge of a reasonable diet	3.337	0.897	−0.108	−0.114	−11.223	0.493**
Q20	I know the standard for good sleep	3.615	0.877	0.053	−0.416	−11.098	0.496**
Q21	I know what healthy habits are	3.776	0.786	0.042	−0.327	−12.246	0.545**
Q22	I know that health includes physical, mental, social adaptation and moral health	3.856	0.819	−0.246	−0.299	−11.369	0.528**
Q23	I have mastered basic physical exercise knowledge	3.499	0.841	−0.094	−0.139	−17.997	0.676**
Q24	I have mastered the knowledge of sports safety protection	3.535	0.808	−0.248	−0.057	−17.939	0.681**
Q25	I know the WHO recommended physical activity guidelines for my age group	2.926	1.059	−0.596	0.056	−12.894	0.558**
Q26	I know the World Health Organization recommended guidelines for sedentary behavior for my age group	2.900	1.104	−0.736	0.055	−12.207	0.528**
Q27	I know that physical activity has many benefits for the human body	4.144	0.836	−0.267	−0.646	−9.981	0.463**
Q28	I think being physically active brings me joy	3.926	0.863	−0.847	−0.214	−19.359	0.675**
Q29	I think being physically active will keep me in better shape	4.160	0.838	0.051	−0.738	−12.545	0.517**
Q30	I think participating in physical activity increases my social interaction	3.874	0.866	−0.947	−0.144	−19.435	0.654**
Q31	I think being physically active makes me healthier	4.259	0.759	−0.573	−0.611	−10.522	0.464**
Q32	I need to increase physical activity to improve my physical test scores	3.994	0.840	−0.330	−0.436	−10.411	0.471**
Q33	Physical exercise is mandatory in schools	4.030	1.051	0.186	−0.910	−3.342	0.144**
Q34	My friends regularly engage in physical activity (e.g., cycling, running, playing ball, etc.)	3.709	0.973	−0.387	−0.370	−15.101	0.565**
Q35	My parents often push me to do physical activities (like biking, running, playing ball, etc.)	3.339	1.077	−0.363	−0.341	−9.848	0.445**
Q36	I enjoy watching various sports (games)	3.327	1.125	−0.569	−0.213	−16.275	0.618**
Q37	I think people who are in good shape are more attractive	3.900	0.952	0.213	−0.680	−8.946	0.421**
Q38	I think people in physical activity are very dynamic	4.146	0.795	0.124	−0.650	−9.481	0.440**
Q39	I am satisfied with my level of physical function	3.259	0.994	−0.272	−0.220	−16.292	0.632**
Q40	I am confident in my physical mobility	3.415	1.021	−0.313	−0.323	−19.964	0.716**
Q41	My body is more attractive than my peers	3.138	1.067	−0.582	−0.009	−16.059	0.649**

**represents a significance level of 1%. **P < 0.01.*

the questionnaire items on their respective factors are >0.40. It shows that the questionnaire has good construct validity. Factor 1 named motor skills, factor 2 named motivation to participate in physical activity, factor 3 named motion skills, factor 4 named confidence to participate in physical activity, factor 5 named cognition of physical activity, factor 6 named physical activity,

TABLE 3 | CSPLQ exploratory factor analysis results ($N = 501$).

Coding	Factor loadings							Commonality
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7	
Q1			0.693					0.552
Q2			0.637					0.681
Q3			0.710					0.770
Q4			0.600					0.743
Q5			0.633					0.698
Q6	0.674							0.714
Q7	0.646							0.613
Q8	0.604							0.557
Q9	0.619							0.556
Q10	0.740							0.618
Q11	0.816							0.751
Q12	0.705							0.636
Q13	0.606							0.677
Q14	0.629							0.703
Q15						0.670		0.660
Q16						0.698		0.654
Q19							0.671	0.655
Q20							0.725	0.668
Q21							0.690	0.709
Q22							0.427	0.584
Q23					0.593			0.665
Q24					0.571			0.654
Q25					0.729			0.751
Q26					0.742			0.770
Q27		0.713						0.574
Q28		0.665						0.652
Q29		0.809						0.689
Q30		0.642						0.622
Q31		0.821						0.693
Q32		0.686						0.534
Q34		0.467						0.564
Q35		0.617						0.517
Q36		0.486						0.543
Q37		0.451						0.521
Q38		0.664						0.620
Q39				0.692				0.685
Q40				0.643				0.717
Q41				0.575				0.621

TABLE 4 | The results of the second-order confirmatory factor analysis of the CSPLQ.

	X^2/df	TLI	CFI	RMSEA
Initial model	4.28	0.823	0.837	0.070
Corrected model	3.07	0.901	0.911	0.062

and factor 7 named cognition of healthy lifestyle. According to the results of factor analysis, the Cronbach α coefficients among the items of each factor were tested. The Cronbach α coefficients of motor skills, motion skills, physical activity, cognition of healthy lifestyle, cognition of physical activity, motivation to participate in physical activity, and confidence to participate in physical activity were 0.867, 0.913, 0.765, 0.768, 0.833, 0.857, and 0.829, respectively. Since there is only one dimension of physical activity remaining in the behavioral field, after consulting experts, the physical activity dimension, motor skills, and motion skills dimensions are combined to form the physical and behavioral field. Therefore, the final CSPLQ is 3 fields and 7 dimensions in total 38 The structure of the assessment for each question.

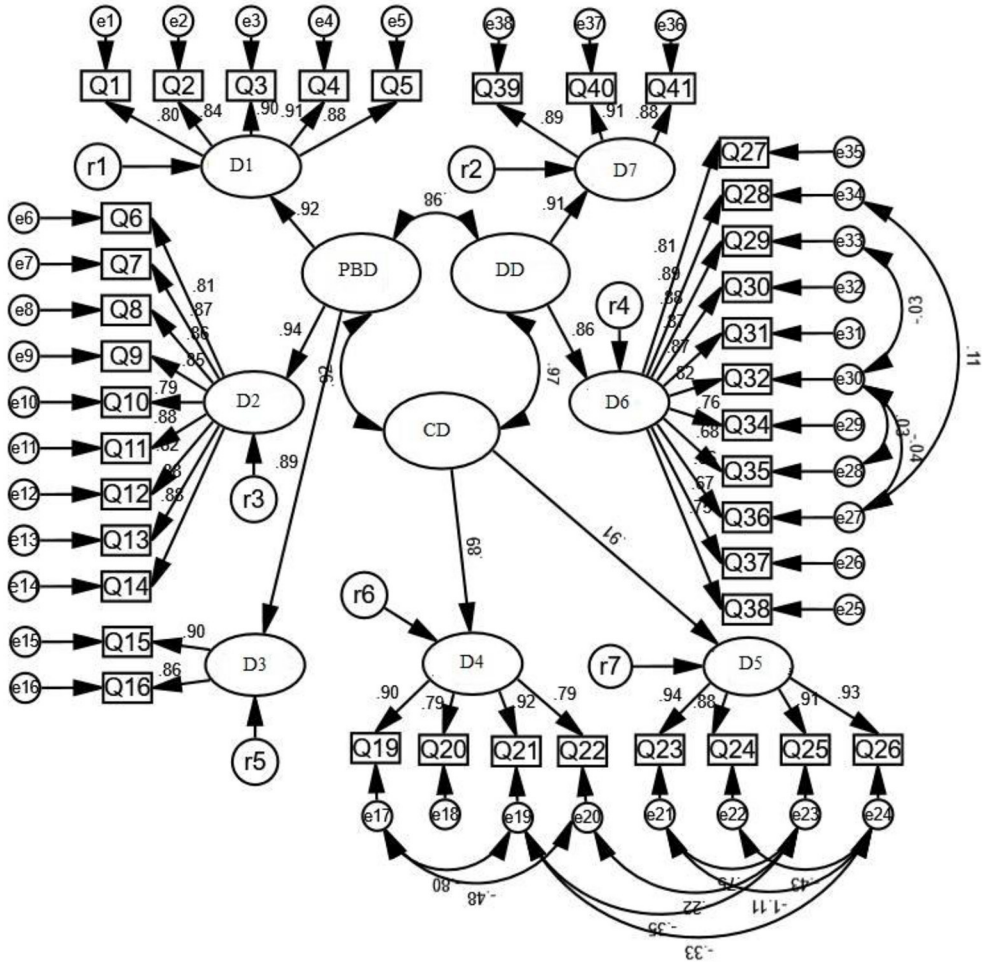

FIGURE 2 | The measurement model of CSPLQ(N = 1,173). D1, Motor skills; D2, Motion skills; D3, Physical activity; D4, Cognition of physical activity; D5, Cognition of healthy lifestyle; D6, Motivation to participate in physical activity; D7, Confidence to participate in physical activity; PBD, Physical and behavioral domain; CD, Cognitive domain; Emotional domain.

Confirmatory Factor Analysis

To verify the stability of the content structure of the CSPLQ, this study used AMOS 23.0 to test Group 2.The evaluation model uses 38 items of CSPLQ as significant variables. Seven first-order factor latent variables (motor skills, motion skills, physical activity, cognition of healthy lifestyle, cognition of physical activity, motivation to participate in physical activity, and confidence to participate in physical activity) were respectively, formed. Among them, three first-order factors of motor skills, motion skills and physical activity constitute a second-order latent variable (physical and behavior domain). Two first-order factors, healthy lifestyle cognition and physical activity cognition, formed a second-order latent variable (cognitive domain). Two first-order factors of motivation to participate in physical activity and confidence to participate in physical activity constitute a latent variable (emotional domain) of a second-order factor. The analysis of the validation factor was performed using the maximum likelihood method.

Confirmatory factor analysis of CSPLQ was carried out using 1,173 survey data of formal test. **Table 4** shows the fitting indexes of the original model and the revised model. The results of data analysis showed that the revised final model had good construct validity (see **Figure 2**). The factor loadings of all item bars are higher than 0.7, indicating that each factor has good convergent validity.

Reliability Analysis

SPSS 22.0 software was used for statistical analysis of the Cronbach α coefficients of the three sub-question tables and the total questionnaire. The Cronbach α coefficients were 0.936, 0.900, 0.915, and 0.961, respectively.

Relationship With Other Variables . This study also looked at the relationship between college students' physical literacy and other variables, including athletic ability, physical condition, physical attractiveness (21), physical fitness, frequency of physical

TABLE 5 | Correlation analysis of CSPLQ with other variables ($N = 1,173$).

Dimension	Exercise ability	Physical condition	Physical attractiveness	Physical quality	Frequency of physical exercise	Duration of physical exercise
Motor skills	0.398**	0.400**	0.279**	0.379**	0.178**	0.241**
Motion skills	0.594**	0.559**	0.446**	0.597**	0.192**	0.290**
Physical activity	0.568**	0.613**	0.406**	0.552**	0.429**	0.342**
Cognition of physical activity	0.137**	0.154**	0.117**	0.156**	0.199**	0.198**
Cognition of healthy lifestyle	0.390**	0.418**	0.331**	0.395**	0.116**	0.213**
Motivation to participate in physical activity	0.390**	0.476**	0.296**	0.388**	0.257**	0.248**
Confidence to participate in physical activity	0.449**	0.482**	0.388**	0.434**	0.180**	0.262**
Physical literacy	0.538**	0.570**	0.413**	0.534**	0.267**	0.322**

**$P < 0.01$.

activity (average weekly voluntary physical activity frequency in the past month), and physical activity duration (every duration of autonomous physical activity). The inspection results showed that the correlation coefficients between the dimensions and total scores of college students' physical literacy and these variables reached a significant level of $P < 0.05$ (**Table 5**).

DISCUSSION

This paper provides evidence for the validity of the CSPLQ. Evidence of content validity is provided for all processes from defining the domain, constructing definitions, generating items for expert review and response processes, content structure analysis, and relationships with other variables (25). For item generation, we referred to existing physical literacy assessment tools because they have good comprehension and a good classification of indicators. However, we found some differences in the structure of the assessment models between the different tools. For example, Australia's structural model of physical literacy assessment consists of four domains: physical, mental, social and cognitive (10). The physical literacy measure developed by the Canadian Care for Life project has five physical, behavioral, cognitive, psychological and social dimensions (26). The physical literacy assessment tool developed by the Canadian Lifetime Sport Program is divided into a professional, coaching, parent and self-test version and contains four main dimensions: physical, behavioral, psychological and cognitive (9). The Canadian Healthy Active Living and Obesity Research Group designed a physical literacy assessment tool that includes physical, behavioral, psychological and cognitive dimensions (9), and Allan constructed a physical literacy assessment tool that focuses on athletes and includes physical, behavioral, cognitive, psychological and social dimensions. In order to obtain more agreement from Chinese scholars, we chose Li 's division of the physical literacy structure, which is currently more agreed by Chinese scholars in this field, and divided the dimensions of physical literacy measurement into four domains: emotional, physical, cognitive and behavioral domains. Most of the experts involved in this study had knowledge related to sport measurement and evaluation or physical literacy research, which was a strength of our study, but given that our study was an initial exploratory study aimed at designing a validated self-report questionnaire on physical literacy, our team endeavored to describe our objectives and methods to the experts in order to provide them with a deeper understanding of the assessment of physical literacy among university students.

We designed a forty-three-item preliminary questionnaire based on the literature and recommendations from a three-person expert panel. The experts were asked to rate and make suggestions on the relevance, clarity and comprehensiveness of the questionnaire items. After this process, two observation points of "daily lying time" and "frequency of physical activity in a week" have been deleted, and two observation points have been modified, such as "body shape preference" being changed to "aesthetic preference," and "activity participation" being changed to "activity" appreciation." Since this process leaves only two entries in both dimensions of our behavioral domain, we naturally expect that it might be less effective later on. But considering that we can also continue to judge their effectiveness through content structure analysis, we keep these dimensions and entries. During the response process, the college students we invited helped to revise the description of the questionnaire, so that our question and answer description methods were more in line with the language habits and acceptance methods of college students. After evaluation, the description of Q24 "I have mastered the knowledge of sports safety protection" was changed to "I have mastered the knowledge of sports safety protection," and the Q36 "I like watching various sports events" was changed to "I like watching various sports activities very much (competition)."

To verify the stability of this structure, we validated it in another sample of university students. The results of the model fit showed that the content structure of the CSPLQ was relatively stable. As there was no Mandarin version of the College Student Physical Literacy Questionnaire for us to make reference to the relationship between the relevant variables, we chose some variables from the Physical Esteem Scale and Physical Activity Behavior to observe the relationship between physical literacy and them. The results showed that the correlation coefficients between physical literacy and other variables, including athletic ability, physical condition, physical

attractiveness, physical fitness, frequency of physical activity and length of physical activity among university students, reached a significant level of $P < 0.05$. This indicates that our questionnaire may be effective in assessing the physical literacy of college students. However, we do not suggest weighted scores for the final scale, and we think this is a question that needs to be further investigated in follow-up studies. Although this study proposes a valid college student self-reported questionnaire to identify college students' physical literacy, there are still some limitations and weaknesses that can be considered for future research. For example, although almost all of our experts know something about physical literacy, none of them has actually done research on physical literacy assessment, so the authority of our experts may affect the validity of our questionnaire. At the same time, we have only two items in one dimension. Although their validity has been verified by other samples, we hope to expand the evaluation items of this dimension in future research. And our sample size is relatively small, and the research sample can be further expanded in the future. Future research could also add test-retest checks to increase the reliability of the questionnaire. Finally, the strength of our research is to open up a new method to objectify the physical literacy of college students, which is a valid self-report questionnaire of college students to identify their physical literacy. Therefore, our study is the first step in developing a standard questionnaire.

CONCLUSION

The CSPLQ has sufficient validity evidence. The development of this tool shows that this tool has validity evidence for its content, response process, internal structure and relationship with other variables.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Review and Approval of the Academic Committee of the Physical Education College of Guizhou Normal University (No. 20210310). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL conceived the study and performed the data analysis and interpretation. LL and NS prepared the manuscript. JYU, CL, LZO, LZA, SL, XG, and JYA were involved in data collection. JH and XZ were involved in the revision and guidance of the paper. All authors have read and approved the final manuscript.

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Assuring Healthy Populations During the COVID-19 Pandemic: Recognizing Women's Contributions in Addressing Syndemic Interactions

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A syndemic framework examines disease interactions and the contributions of structural, social, economic, and environmental factors that synergistically interact to contribute to adverse health outcomes. Populations residing in environments with structural susceptibilities experience health disparities and syndemics to a greater extent than their less vulnerable counterparts. The interactions among the social determinants of health (SDoH) and the COVID-19 pandemic have had different results for marginalized populations and have worsened health outcomes for many in this synergistic pandemic. Also, the exposome, the exposure measures for an individual over their lifetime and how those exposures relate to the individual's health, may help to explain why some populations experience more serious cases of COVID-19 compared to other groups. The purpose of this perspective is to: (1) examine the relationship between the syndemic model and the SDoH-exposome; (2) highlight, *via* specific examples, the contributions of female health professionals to SDoH and the COVID-19 syndemic in response to the Women in Science Research Topic, and (3) propose health policy to address syndemic-exposome interactions to help mitigate or prevent public health challenges. By investing in policies that assure health for all populations, the investments could pay dividends in the form of a less severe syndemic next time since we are starting from a place of health and not disease. Lastly, due to the magnification of underlying societal inequities laid bare during the COVID-19 syndemic, we support the expansion of the disease-focused syndemic model to include societal syndemics, such as systemic racism.

Keywords: social determinants of health, exposome, healthy populations, Women in Science, COVID-19, syndemic, systemic racism

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INTRODUCTION

A prominent figure in the United States (U.S.) public health system in the late nineteenth and early twentieth centuries was Charles-Edward Amory Winslow (1). Winslow defined public health in 1920 and his description of this civic-oriented, and interdisciplinary field is still in use today:

> "Public Health is the science and the art of preventing disease, prolonging life, and promoting physical health and efficiency through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and preventive treatment of disease, and the development of the social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health; organizing these benefits in such fashion as to enable every citizen to realize his birthright of health and longevity" (2).

From this eloquent definition arises the essential services of public health which align with the assessment, policy development, and assurance functions of public health that are responsible for preventing disease and injury, promoting health and wellbeing, and protecting population health (3). These are core concepts and actions that have helped public health systems at the local, state, national, and international levels manage complex public health challenges, for example, childhood lead poisoning, foodborne outbreaks, obesity, the opioid epidemic, and the COVID-19 pandemic.

Our knowledge and practice of public health has evolved to where we now consider the contributions of the social determinants of health (SDoH) to community health issues. The SDoH are defined as those conditions present in the places we live and spend our time to work, learn, and play (4). Representative examples of SDoH include economic stability (e.g., employment, income, and medical bills); neighborhood and physical environment (e.g., housing, transportation, and walkability); education (e.g., literacy, language, and higher education); food (e.g., access to healthy food choices and hunger); community and social context (e.g., social integration, support systems, and stress); and healthcare system access (e.g., health coverage, provider availability, and quality of care) (5). Approximately 80% of health outcomes are estimated to be due to the SDoH. Specifically, social, and economic factors account for 40% of health outcomes and health behaviors and the physical environment account for 30% and 10% of health outcomes, respectively. Clinical care is estimated to account for 20% of health outcomes in populations. Therefore, the SDoH are non-medical factors that can have a significant and broad effect on health outcomes and quality of life indicators (4, 6). Addressing the SDoH is fundamental to eliminating health disparities, promoting health equity, and improving overall population health outcomes (7).

The SDoH and their contributory role to a population's health status have compounded the extent to which chronic illnesses and communicable diseases have distressed populations. This impact is evident during the current COVID-19 pandemic which began in the U.S. in January 2020 and has disproportionately affected racial and ethnic minorities (8). Specifically, elevated rates of COVID-19 morbidity and mortality have been demonstrated in African American, Native Americans, and LatinX populations compared to their White counterparts. Research suggests that SDoH contribute to these findings (8). For example, these racial and ethnic minorities often experience decreased access to healthcare and living and employment conditions that predispose them to exposure to SARS-CoV-2 (8). Environmental and socio-economic factors and structural racism have contributed to the COVID-19 risk in these vulnerable populations since the social systems in place in U.S. communities often perpetuate practices that promote an inequitable distribution of resources due to multiple levels of racism (e.g., institutional racism, personally-mediated racism, and internalized racism) (9, 10). Comparatively, Blacks have experienced the highest COVID-19 diagnoses rates in the United Kingdom (U.K.) and ethnic minorities (specifically Asian populations) have had an elevated mortality rate compared to their White British counterparts (11). In both the U.S. and the U.K, the presence of pre-existing comorbidities (e.g., South Asian populations experience high rates of diabetes and cardiovascular disease; Blacks experience high rates of hypertension) and socio-economic and geographical factors, population density, housing quality, and occupation may account for the observed health disparities during the COVID-19 pandemic (9, 12).

These interactions among the SDoH have played a role in the COVID-19 pandemic in different ways for marginalized populations and have worsened health outcomes for many in this synergistic pandemic, called a syndemic (13). The purpose of this perspective is to: (1) examine the relationship between the syndemic model and the SDoH-exposome; (2) highlight, *via* specific examples, the contributions of female health professionals to SDoH and the COVID-19 syndemic in response to the Women in Science Research Topic, and (3) propose health policy to address syndemic-exposome interactions to help mitigate or prevent public health challenges.

SYNDEMIC INTERACTIONS

Syndemic Defined

The synergistic interactions among disease and the contextual social environment (i.e., SDoH) in which they occur can result in a syndemic. More specifically, a syndemic is described by the coming together of two or more health conditions (e.g., chronic illness and infectious disease) and their adverse interactions with each other and the SDoH that can provide the milieu for enhancing vulnerabilities, magnifying inequities, and worsening health outcomes for marginalized populations (14–16). A syndemic framework examines disease interactions and the contributions of structural, social, economic, and environmental factors that synergistically interact to contribute to adverse health outcomes for individuals and whole populations (16, 17). Singer first introduced the term *syndemic* in the 1990s when he described the interactions among substance abuse, violence, and AIDS (SAVA syndemic) (15). Singer identified the criteria necessary for a syndemic: (1) grouping of two or more health conditions or diseases in a population; (2) social and contextual factors that allow for the biological interactions to occur and for the development of adverse health outcomes, and (3) disease interactions that lead to negative outcomes (e.g., health, social, and behavioral) for the affected population and increases their health burden (15, 16). Other syndemics identified and studied by women researchers include the HIV, malnutrition, food insecurity syndemic and the violence, immigration, depression, type-2-diabetes, abuse syndemic (VIDDA syndemic) among

Mexican women immigrants (15, 16). Syndemics are not restricted to communicable and chronic diseases and may be heightened by health inequality attributable to poverty, structural violence, and stigmatization (16). For example, research has demonstrated that children who encounter adverse experiences during childhood, such as living in a violent neighborhood or witnessing violence in their living environment are three times more likely as children who do not experience similar violence to be diagnosed with asthma. This synergistic relationship of living with fear, violence, and asthma are representative of a syndemic often observed in urban environments (16, 18).

Literature Review

To respond to the Women in Science Research Topic, we examined the contributions of female researchers to the COVID-19 syndemic. We examined GALE Biography, Historical Abstracts, and PubMed databases. The historical databases were reviewed with an emphasis on the time period: 1800-1918; 1919-1950 (WW1-WW2); and Post-WWII (1951-present). Two U.S. government reports featuring women and minority scientists were also utilized (19, 20). Searches were conducted from November 2021–January 2022.

For the GALE Biography and Historical Abstracts databases, we used the following search strings: ["public health" OR epidemiolog*) AND (pioneer* OR famous)]; and ["syndemic" AND ("women" OR "female") AND (pioneer* OR famous)], which identified 111 citations. We excluded citations if they did not focus: (a) on women's contributions; (b) on public health; or (c) on an English translation. Duplicate citations were excluded. A total of 23 citations resulted, highlighting women's significant contributions to public health in clinical, research, and policy/advocacy domains from the pre-Industrial Revolution period through the Post WW-II period.

For the PubMed database, using the search phrase, "syndemic and public health and female authors", 69 articles were identified with 51 including the term "syndemic" in the abstract, title, or narrative of the article. Using the search phrase, "COVID-19 syndemic and public health and female authors", 7 of the 51 published articles were identified. The articles in the PubMed database identified the long-standing SAVA syndemic and more recently the COVID-19 syndemic with the range of COVID-19 syndemic articles published between 2020 and 2021.

Women Health Professionals' Contributions to the SDoH and Syndemics

The historic literature review identified female health professionals' "pre-syndemic" contributions, which are often unrecognized in public health textbooks and curricula. The authors, who are both female, further note that this work provided a strong foundation upon which the essential public services of contemporary public health could be built. For example, female health professionals advanced the fields of public health nursing across the globe, contributed to our understanding of the zoonotic transmission that foreshadowed the contemporary One Health model, campaigned for gender-sensitive policies, established community clinics focusing on the overall wellness of the community, and expanded our scientific knowledge through research in fields such as bacteriology and immunology. The work of these women foreshadowed the need to address syndemics *via* a SDoH perspective.

The relationship between the SDoH and the COVID-19 syndemic is also evident in the results from the literature search which identified the following select global contributions from women health professionals:

- Active dengue (endemic vector-borne disease) infection and co-infection with SARS-CoV-2 in Brazil resulted in severe pulmonary conditions and contributed to burdening an overwhelmed healthcare system and warranting preventive measures (21); the syndemic nature of dengue and COVID-19 warrants a promotion of preventive measures and further investigation into their epidemiological and clinical interactions in Peru (22).
- Mentoring as a solution to develop women and underrepresented racial and ethnic minorities as faculty and leaders in U.S. academic medicine settings during the racism and COVID-19 syndemics (23).
- Preventive measures to restrict physical contact during the COVID-19 syndemic has affected healthy nutrition practices (24).
- The racism and COVID-19 syndemics and their associated vulnerabilities need to be considered for Black women and pregnant women in the U.S. Prevention approaches should consider SDoH that contribute to the grouping of vulnerabilities (25).
- Essential workers who reside in middle-income countries (i.e., Brazil and Spain) with elevated rates of inequality may face challenges during the COVID-19 syndemic (e.g., mental health support) due to COVID-19 and SDoH interactions (26).
- A syndemic framework should be applied to populations co-infected with COVID-19 and HIV in Nigeria. Also, there is a need to strengthen healthcare delivery services in response to the current public health challenges (27).

Based on the work described above and prior research in this area, populations residing in environments with structural susceptibilities experience health adversities and syndemics to a greater extent than their less vulnerable counterparts which warrants a review of the contributory upstream determinants (e.g., social, economic, and political factors) (17).

Women researchers have proposed that the interactions between the COVID-19 syndemic and the SDoH engage in a bi-directional relationship (28). In this relationship, structural determinants (e.g., poverty, and violence); sociocultural determinants (e.g., lifestyle, family conflict, and support); socioeconomic determinants (e.g., employment and access to health care); and individual determinants (e.g., health behavior and self-efficacy) interact with each other. For example, if one is employed in a service industry as an hourly employee then they probably need to keep going to work due to the lack of sick time. If they do not work, they will not be paid which means they can't provide food and shelter for themselves or families. As a result, many of these people put themselves at risk of exposure to SARS-CoV-2 because the interactions of the SDoH with the COVID-19 syndemic removes their choice to prioritize their health (15, 17).

To assure the health of populations experiencing these syndemics, the authors propose, based on female health professionals' contributions in this area, that significant reform of public health policy in the U.S. occurs that assures a basic standard of living where housing is affordable, a minimum wage allows for healthy food choices, and universal healthcare, as a few starting points. Such systemic change will take years but if the COVID-19 syndemic has taught us anything, it is that to survive the next pandemic, with the least amount of morbidity and mortality, will require starting with a healthy population and not the magnitude of widespread inequity that currently exists in the U.S.

Supplementary Table 1 highlights the myriad contributions of female health professionals to the pre-syndemic and COVID-19 syndemic domains.

Syndemics and the Exposome

Another area that warrants attention is the role of the exposome in syndemics. The exposome, coined by Wild in 2005 (29) is intended to complement the genome, and is defined as the exposure measures for an individual over their lifetime and how those exposures relate to the individual's health (30, 31). Exposures can include determinants in the form of the natural environment (e.g., air pollution and toxicants), built environment (e.g., greenspace and walkability) and social environment (e.g., neighborhood deprivation and lifestyle) (32, 33). These interactions have been shown to have negative effects on asthma, cardiovascular disease, diabetes, and hypertension which have been reported as co-morbidities for severe COVID-19 (32, 34–36).

The exposome may help to explain why some populations experience more serious cases of COVID-19 compared to other groups (37). Studies have shown that SARS-CoV-2 binds to a human angiotensin converting enzyme 2 (ACE2) receptor located on the epithelial cells of the lungs, blood vessels, brain, kidney, and intestines (38). Exposure to environmental toxins (e.g., air pollution), lifestyle behaviors (e.g., high fat diet), and underlying disease (e.g., diabetes) can affect the expression of ACE2 and possibly increase the severity of the SARS-CoV-2 infection (37). Therefore, it is possible that gene and environmental interactions could account for varying rates of COVID-19 susceptibility among different racial and ethnic groups (37–39).

Female scientists are also contributing directly to exposome research. For example, the Hercules project at Emory University was funded by the U.S. National Institute of Environmental Health Sciences in 2013 to support exposome research. Several women participated in discovering, implementing, and evaluating the application of the exposome concept to advance our understanding of how gene-environment interactions affect population health (40). For example, women researchers have also been studying how certain air pollutants may affect the brain and increase the risk for dementia. The study combines survey data with traffic-related air pollution data based on geographic location, enabling researchers to evaluate relationships between air pollutant mixtures and stages of cognitive decline.

Another female researcher has been developing a novel model to assess the effects of metal exposure on fetal lung development. The research examines whether pregnant women's exposure to heavy metals, such as cadmium and arsenic, interferes with fetal lung development. This study advances our understanding of how environmental exposures that occur prior to birth may contribute to pulmonary disease. Additional women researchers are examining the intersection of genomics, cultural competency, and health disparities, calling for the establishment of culturally competent systems of care (41).

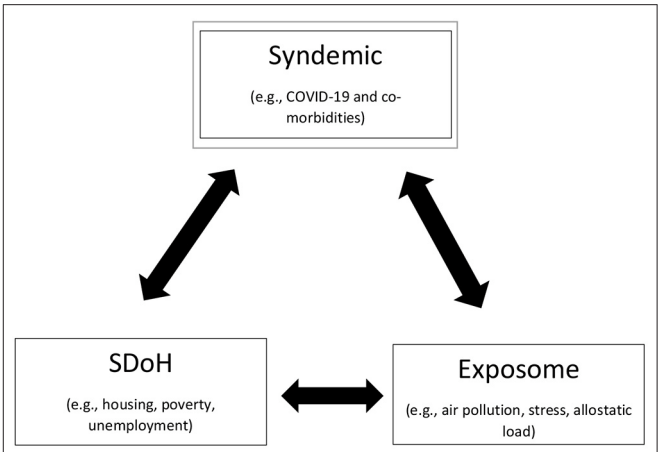

FIGURE 1 | Syndemic interactions among the SDoH-exposome. We propose that in addition to a bi-directional relationship between SDoH and a syndemic, that there is potential for a bidirectional relationship between the exposome and a syndemic and a bi-directional relationship between the exposome and SDoH. For example, populations residing in overcrowded, poor quality housing that is zoned between an auto-body shop and a crematorium in an urban environment may be living with historical housing segregation practices. This population may work in a service occupation earning an hourly wage, may be exposed to air pollutants and toxicants *via* their living environment and the public transportation system that is necessary to attend work, and run errands. The local food source is a centralized convenient store which does not provide a reliable supply of fruits and vegetables at an affordable price. This population resides in a high crime neighborhood where the murder rate, gang violence, and illegal drug use are increasing. These SDOH-exposome interactions make one more susceptible to the COVID-19 syndemic due to the multitude of exposures encountered. In turn, these conditions contribute to a syndemic hotspot of COVID-19, substance misuse, and toxic stress accelerating negative environmental exposures (e.g., medical waste, hypodermic needles, increased carbon emissions and worsening air quality) that act as force multipliers for the population's allostatic load.

Building on the work of female health professionals who have preceded them, the authors of the present study propose that in addition to a bi-directional relationship between SDoH and a syndemic, that there is potential for a bi-directional relationship between the exposome and a syndemic and a bi-directional relationship between the exposome and SDoH (**Figure 1**). For example, populations residing in overcrowded, poor quality housing that is zoned between an auto-body shop and a crematorium in an urban environment may be living with historical housing segregation practices. This population may work in a service occupation earning an hourly wage, may be exposed to air pollutants and toxicants *via* their living environment and the public transportation system that is necessary to attend work, and run errands. The local food source is a centralized convenience store which does not provide a reliable supply of fruits and vegetables at an affordable

price. This population resides in a high crime neighborhood where the murder rate, gang violence, and illegal drug use are increasing. These SDOH-exposome interactions make one more susceptible to the COVID-19 syndemic due to the multitude of exposures encountered. In turn, these conditions contribute to an evolving syndemic hotspot of COVID-19, substance misuse, and toxic stress accelerating negative environmental exposures (e.g., medical waste, hypodermic needles, and increased carbon emissions) that act as force multipliers for the population's allostatic load (42).

The environment has been reported to be responsible for ∼70–90% of chronic disease while one's genome is purported to be responsible for 10–30% of chronic disease (43). Thus, a review of the exposome may complement a syndemic mitigation approach that considers the SDoH, political, and economic factors that propagate biological and societal epidemics.

DISCUSSION

C-E.A. Winslow's public health definition is still applicable today when addressing complex public health challenges. The COVID-19 pandemic, arguably one of the most complex public health challenges of the twenty-first century to date, has been described as a syndemic that is compounded by pre-existing underlying disease and the SDOH-exposome. These syndemic interactions may worsen the morbidity and mortality for marginalized populations but these relationships could also direct our limited resources to mitigating or preventing adverse health effects for future public health challenges. For example, there is a role for policy, or as Winslow calls the "social machinery" (1), to improve the conditions in which people live, work, and play. Policy interventions could assure healthy populations by providing equitable access to quality healthcare, affordable and safe housing, guaranteed minimum living wage, and healthy and affordable food options. By investing in policies that assure health for all populations, the investments could pay dividends in the form of a less severe syndemic next time since we are starting from a place of health and not disease. Recognizing women's contributions to population health and developing policies that support pathways of opportunity for women to assume leadership roles in institutions such as government, higher education, and healthcare will enable us to work toward favorable SDoH-exposome interactions that may reduce the burden of future syndemics. Examples of such policies include paid maternity/paternity leave, childcare, elder-care support, access to safe reproductive healthcare services, living-wage policies, and workplace policies ensuring safety and work-life balance (44).

The COVID-19 syndemic has made visible underlying, pervasive systemic flaws, such as structural racism, in the education, housing, and employment sectors, and has forced public health to acknowledge racism as a crisis. A female researcher calls for, and the authors agree, that the concept of syndemics needs to move beyond disease-oriented syndemics and expand to include societal epidemics: "that social phenomena such as direct violence (e.g., interpersonal violence, genocide, ethnic cleansing, colonialism, and imperialism) and structural violence (e.g., poverty, racism, historical trauma, and political disenfranchisement) are widespread and adversely affect health in many…communities, thus meeting the definition of an epidemic" (45).

Structural or institutional violence, specifically systemic racism, refers to practices that are embedded in local, state, and federal policies and provide an advantage to certain populations and not others (10, 46). The interventions to address systemic racism require structural interventions *via* policy reform across public and private sectors including, but not limited to, health, education, employment, and the criminal justice system (46). The development, implementation, and assessment of equitable economic policies that address poor quality housing, unemployment, poverty, and racial segregation could help to reduce socio-economic inequalities among racial and ethnic minorities and help to minimize the burden of disease (46, 47).

The bi-directional relationship among the SDoH, including the political and economic determinants, exposome and a syndemic, whether biological or societal in nature, can be synergistic at a population level and have widespread consequences (48). The spread of a disease or selective behaviors in an epidemic or pandemic "always follow the fault lines of society" (49) and depending on the syndemic interactions, the inequities may become visible or magnified despite always having been present as has occurred during the COVID-19 syndemic.

To serve as a call to action to address syndemic interactions and assure healthy populations in the face of complex public health challenges, we have highlighted work conducted globally by female healthcare professionals that have informed our pre-syndemic environment and the current COVID-19 syndemic. As a result of this work, we call for transformative changes across governments, systems, and infrastructures to support gender-sensitive policies that will improve the SDoH-exposome interactions as key drivers of health (50). As the COVID-19 syndemic has demonstrated, *via* the contributions of many women researchers, all populations are interconnected, and addressing the interactions that contribute to preventable morbidity and mortality will facilitate reductions in the global burden of disease for all people.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

RC proposed the topic for discussion and took the lead in writing the article. RC and SA co-developed the manuscript outline. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.856932/full#supplementary-material

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Infectious Disease Control and Management in Ethiopia: A Case Study of Cholera

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Cholera remains a significant public health problem among the vulnerable populations living in many resource-limited settings with poor access to safe and clean water and hygiene practice. Around 2.86 million cholera cases and 95,000 deaths are estimated to occur in endemic countries. In Ethiopia, cholera has been one of the major epidemic diseases since 1634 when the first cholera outbreak was recorded in-country. Several cholera epidemics occurred with recent outbreaks in 2019–2021. Cholera has been often reported as acute watery diarrhea due to limited diagnostic capacity in remote areas in Ethiopia and sensitivities around cholera outbreaks. The government of Ethiopia has been executing several phases of multi-year health sector development plan in the past decades and has recently developed a national cholera control plan. Here, we aim to present the existing cholera control guidelines and health system in Ethiopia, including case detection and reporting, outbreak declaration, case management, and transmission control. Challenges and way forward on further research and public health interventions are also discussed to address the knowledge and health service gaps related to cholera control in Ethiopia.

Keywords: cholera, OCV, national cholera control plan, case detection, case management, outbreak response, health system, Ethiopia

INTRODUCTION

Cholera is a diarrheal disease caused by the gram-negative bacteria *Vibrio cholerae (V. cholerae)* infection that can cause extreme loss of fluid and severe dehydration. The disease remains a significant public health problem for people with poor access to safe and clean water, sanitation, and hygiene (WaSH) practice; a proxy indicator of a country's lagging socio-economic development. Around 2.86 million cholera cases and 95,000 deaths are estimated to occur in endemic countries in 2015 (1–3). Of the countries with over 1,000 cholera deaths annually, all are in Africa except for India, Bangladesh, Haiti, and Sudan (1, 4). According to the recent Global Burden of Disease (GBD) Study, diarrhea was the eighth leading cause of death among all ages (1.66 million deaths, 95% uncertainty interval) in 195 countries worldwide in 2016; overall diarrheal mortality was 22.4 deaths per 100,000 with higher rates among children younger than 5 years (70.6 deaths per 100,000) (5). *V. cholerae* has been the third leading cause of diarrhea mortality among all ages,

responsible for 107,290 deaths, which included 52,232 deaths among children <5 years of age (5). Further, approximately 750,000 of a total of 4.3 million deaths of African children up to 4 years of age are reportedly associated with diarrheal diseases (6). A recent analysis on childhood diarrheal morbidity and mortality in Africa during 2010 and 2015 exhibited diarrheal diseases as the third leading cause of disease and death in children younger than 5 years of age, responsible for an estimated 30 million cases of severe diarrhea and 330,000 deaths in 2015 (7).

As the SARS-CoV-2 (COVID-19) pandemic hit the world since the beginning of 2020, cholera epidemics coexisted with the pandemic. The number of cholera cases reported to the World Health Organization (WHO) has dropped significantly in 2020; with reports of 323,320 cholera cases and 857 deaths in 27 countries among 80 countries that reported cholera, 65% decrease compared to 2019 whereby 923,037 cases and 1,911 deaths were reported globally (8). This phenomenon can be explained in several aspects. The COVID-19 pandemic has also put increased pressure on existing health systems in cholera-endemic countries (4). It is highly likely that the national and local public health surveillance system and laboratory diagnostic capacities for cholera detection and reporting may have been over-stretched, as existing healthcare personnel and resources are prioritized for COVID-19 surveillance and pandemic control (8). The promotion of personal hygiene and hand washing, social distancing, and even lock down measures in some countries during the COVID-19 pandemic may have had some impact on the cholera transmission dynamics (8). Albeit the overall decrease in the number of global cholera cases reported during the first year of COVID-19 pandemic in 2020, Ethiopia has been reporting cholera epidemics in 2019 and throughout 2020 and 2021 (8, 9).

In Ethiopia, cholera has been one of the major epidemic diseases for centuries. Since 1634, when the first cholera outbreak was recorded in Ethiopia with the name of *fangal* (subsequently used for cholera) (10), existing studies suggest that at least five cholera epidemics followed in Ethiopia in the 19th and early 20th centuries, including several outbreaks in more than one waves; cholera outbreaks between 1831–1836 (two separate waves), 1856 and 1866–1867, during the great famine in 1889–1892 (two waves), and 1906 (10, 11) Since 1970, when the seventh global cholera pandemic driven largely by the O1 serogroup and the El Tor biotype reached Africa (12), cholera cases have been subsequently reported in Ethiopia. A comprehensive phylogenetic analysis of contemporaneous African *V. cholerae* strains between 1966 and 2014 exhibited past cholera epidemics in Africa attributable to a single expanded lineage introduced at least 11 times since 1970 (12). The two El Tor strains were introduced to Africa in 1970 with serotype Ogawa in West Africa and serotype Inaba in East Africa particularly in Ethiopia (12). The 1970 *V. cholerae* isolates from Ethiopia are likely associated with importation from the Middle East, and the subsequent cholera epidemics in the continent linked to the multidrug resistant (MDR) sublineages from parts of Asia since 2000 (12) More recent publications on cholera outbreaks in Ethiopia elaborated frequent cholera outbreaks in parts of Ethiopia associated with the 1985–1986 epidemic in the Horn of Africa; Ogawa strain in Ethiopia caused or linked to outbreak in Northern Somalia (13, 14). Cholera re-emerged in Ethiopia in 1993 that affected both urban and rural areas of regional states of Oromiya and Somali and the Addis Ababa, and subsequently in 1994 albeit irregular institutional reporting of cholera cases (15). No extensive recurrence of cholera was reported in 1996 and 1997, but an epidemic reappeared in 1998 and in the 2000s; case series in 2004 and large outbreak in 2006 (15). Reports of cholera cases in the 1990s and 2000s remained irregular in Ethiopia and often reported as acute watery diarrhea (AWD) (16), but cases have been reported continuously with most recent cholera epidemic declarations by the Ethiopian government in 2019, 2020 and 2021 (17).

In response to these past cholera outbreaks in Ethiopia, the government has been taking measures for cholera outbreak investigation and control, setting-up of cholera treatment centers and case management. In 2019, the Ethiopian government has also requested the World Health Organization (WHO) Oral Cholera Vaccine (OCV) International Coordinating Group (ICG) for the emergency use of OCVs, and utilized the bilateral diplomatic channel to get support from the government of Republic of Korea with OCV doses for large-scale reactive mass vaccination campaigns to control cholera outbreaks. More recently, the government of Ethiopia has also officially expressed the commitment for national cholera elimination roadmap and developed a comprehensive multi-sectoral national cholera control plan (NCP) (18). This multi-year government plan entitled the "Multi-sectorial Cholera Elimination Plan, Ethiopia 2021–2028" has been developed (18) in alignment with the WHO Global Task Force for Cholera Control (GTFCC) 'Ending Cholera – Global Roadmap to 2030' (19), and submitted to the WHO GTFCC in 2021 for endorsement.

Here, we aimed to review the existing cholera control guidelines in Ethiopia, which includes: Section 1 on cholera surveillance and outbreak investigation covering cholera case detection and reporting and outbreak investigation; Section 2 on cholera outbreak control and management, focused on responsibilities of government stakeholders at different levels and health facilities, outbreak response, case management, transmission control, and use of OCV; Section 3 on the Ethiopian government's commitment for cholera control and elimination in Ethiopia; and Section 4 on challenges and way forward to enhance cholera control and prevention in the country. Our intended audiences are national public health leaders and managers, policy makers in health and finance ministries, public health professionals involved in sentinel-based surveillance and community engagement for early cholera case detection, outbreak preparedness and effective outbreak controls, and other national and global stakeholders in bilateral and multilateral aids or technical supports.

TABLE 1 | National public health laboratories in Ethiopia.

Laboratories[1]	Lab type	BSL[2]	Lab location	Areas covered	Population of areas covered[3]	Cholera case diagnosis experience	Cholera case diagnosis capacity
Ethiopian Public Health Institute (EPHI) National Reference Laboratory[4]	National Reference laboratory	BSL 2	Addis Ababa (Capital city)	Nation-wide	103 million	Yes	RDT culture serotyping (PCR)
Armauer Hansen Research Institute (AHRI) Laboratory[5]	National Clinical Research Reference laboratory	BSL 2	Addis Ababa (Capital city)	Nation-wide	103 million	Yes	RDT culture serotyping (PCR)
Addis Ababa Regional Laboratory	Regional laboratory	BSL 2	Addis Ababa	Addis Ababa	3.8 million	Yes	RDT culture
Adama Public Health Research & Referral Laboratory	Regional Laboratory	BSL 2	Adama zone	Oromia region	39.0 million	Yes	RDT culture
Afar Public Health Institute Laboratory	Regional laboratory	BSL 2	Semera	Afar region	1.9 million	Yes	RDT culture
Amhara Public Health Institute Laboratory	Regional laboratory	BSL 2	Amhara Bahir Dar	Amahara region	22.5 million	Yes	RDT culture
Amhara Public Health Institute Laboratory - Dessie Branch	Regional laboratory	BSL 2	Dessie	Amhara region (South Wello zone North Wello zone North Shewa zone Oromo Special zone Waghimra-zone)	8.2 million	Yes	RDT culture
Benishangul Gumuz Regional Laboratory	Regional laboratory	BSL 2	Assossa	Benishangul-Gumuz region	1.2 million	Yes	RDT culture
Diredawa Regional Laboratory	Regional laboratory	BSL 2	Dire Dawa	Dire Dawa city	521,000	Yes	RDT culture
Gambella Regional Laboratory	Regional laboratory	BSL 2	Gambella	Gambella region	492,002	Yes	RDT culture
Harari Regional Laboratory	Regional laboratory	BSL 2	Harar	Harar region	270,000	Yes	RDT culture
Nekemte Public Health Research and Referral Laboratory	Regional laboratory	BSL 2	Nekemte, Oromia Regional State	East Wollega West Wollega Horo Gudru Wollega Kelem Wollega Iluabbabor Bunno Bedele Jimma Zone West Shewa zone Jimma town Nekemt town Ambo town	11 million	Yes	RDT culture

(Continued)

TABLE 1 | Continued

Laboratories[1]	Lab type	BSL[2]	Lab location	Areas covered	Population of areas covered[3]	Cholera case diagnosis experience	Cholera case diagnosis capacity
Shashemene Public Health Research and Referral Laboratory	Regional Laboratory	BSL 2	Shashemene	West Arsi zone Borena Guji West Guji Shashemene town Bishan guracha town	7 million	No	None
Somali Regional Laboratory	Regional laboratory	BSL 2	Jigjiga	Somali region	6.4 million	Yes	RDT culture
Southern Nations, Nationalities, and Peoples' Region (SNNPR): Regional State Public Health Laboratory	Regional laboratory	BSL 2	Hawassa	SNNPR region Sidama region	21.0 million	Yes	RDT culture
Tigray Health Research Institute Laboratory	Regional laboratory	BSL 2	Mekele	Tigray region	5.6 million	Yes	RDT culture

[1]The list of national public health laboratories compiled by the EPHI and AHRI and also referred to the Ethiopian National Accreditation Office (ENAO) official webpage; [2]BSL, Biosafety level; [3]Ethiopia Population Projection Wereda as of July 2021 | Central Statistics Agency official webpage (http://www.statsethiopia.gov.et/population-projection); [4]EPHI laboratory, Established in 1996 as the Ethiopian Health and Nutrition Research Institute (EHNRI) laboratory, and the name changed in 2013 as the EPHI laboratory. Mandated to increase and maintain quality assurance of public laboratories; enhance and implement quality management system of public laboratories; and strengthen laboratory capacity for referral and back-up testing services; [5]AHRI laboratory, Mandated to foster evidence-based decision making; improve medical research capacity; foster health innovation and technology transfer; promote local and international participatory research; and improve efficiency of system and ensure accountability.

SECTION 1: CHOLERA SURVEILLANCE AND OUTBREAK INVESTIGATION IN ETHIOPIA

Cholera Case Detection and Reporting

The Guideline on Cholera Outbreak Management in Ethiopia published by Ethiopian Public Health Institute [EPHI; former Ethiopia Health and Nutrition Research Institute (EHNRI)] states cholera as a mandatory notifiable disease (20). All suspected cholera cases need to be reported upon identification. Suspected case is defined as any person 5 years of age or more with profuse AWD and vomiting. Confirmed case of cholera, defined as suspected case with *V. cholerae* O1 or O139 isolated from stool, is sufficient for an outbreak to be declared (20) More specifically, cholera outbreak declarations are made: in cholera epidemic areas, when a patient aged 5 years or more who develops AWD, with or without vomiting is detected; and in an area where cholera is not known to be present, when a patient aged 5 years or more who develops severe dehydration or dies from AWD is detected (20). This implies the importance of existing public health disease surveillance system and reporting capacity. Cholera case detection and outbreak declaration is also closely associated with the healthcare seeking behaviour of local populations and cholera rapid diagnostics and laboratory confirmation ability. In Ethiopia, there are 16 public health laboratories nation-wide; EPHI National Reference Laboratory located in Addis Ababa, Armauer Hansen Research Institute (AHRI) laboratory in Addis Ababa for handling medical research samples, and 14 Regional Laboratories across the country (**Table 1**).

Outbreak Investigation

When a suspected cholera case is reported, a multidisciplinary outbreak investigation team [Rapid Response Team (RRT)] should be organized by the EPHI and an outbreak investigation initiated within 3 hours, according to the EPHI (EHNRI) guideline (20). The RRT is composed of a clinician, lab technician, communication expert, epidemiologist, and environmental health expert (20). The team conducts field assessments to verify reported cholera cases, determine magnitude of cholera outbreak, collect specimens for laboratory confirmation of *V. cholerae*, assess cholera outbreak response capacity at local level, identify high-risk groups, investigate source of contamination, conduct simple on-site control measures, provide emergency treatment supplies, and report findings of outbreak investigation (**Table 2**) (20). The following variables are to be collected and/or reviewed from the available health facility register: name, age, sex, address, symptoms, date of onset of illness, date treated, treatment provided, treatment outcome (alive, dead, referred), specimen collection status, any risk related data, and index case tracing (20) At community level, interviews of household members and neighbors of cholera cases are to be conducted to assess any recent travel history, contacts with suspected cholera cases or/and ill persons with diarrhea, recent attendance at a funeral (and cause of death of deceased), water sources (drinking, bathing, cleaning kitchen utensils), food

consumption history, occupation, and any other risk factors for cholera transmission (20).

SECTION 2: CHOLERA OUTBREAK CONTROL AND MANAGEMENT IN ETHIOPIA

Responsibilities at Various Government Levels and Health Facilities

Cholera detection and outbreak control include government roles at Woreda, Zone/Regional and Federal levels, responsible for providing adequate and timely support with technical expertise, supplies and resources, situation analysis, decision makings, communications and reporting, etc. (**Figure 1**). When a cholera outbreak is suspected or confirmed, an Epidemic Control Committee (ECC) must be convened immediately and conduct regular meetings to review responsibilities of stakeholders and track progress in outbreak control (20). The committee members are composed of representatives from multi-sectors and partners for a comprehensive cholera control and prevention approach. Notably, the EPHI (EHNRI) Guideline recommends an inter-country ECC if cholera outbreaks occur near the national border (20). The ECC is also mandated to meet regularly in non-epidemic periods for epidemic preparedness and prevention activities (20).

Outbreak Response

The key objectives of cholera outbreak response are reducing deaths attributable to cholera and preventing new cholera cases. To achieve these goals, following activities are critical: clear roles and responsibilities at various government and health facility levels, disease surveillance capacity at health facilities, accurate and quick diagnosis at laboratories, quality documentation and reporting, adequate and timely decision-making and allocation of human resources and supplies, proper case management, rapid outbreak investigation and community sensitization to control sources of potential transmission and risk factors, etc. Proper cholera case management requires setting up appropriate Cholera Treatment Centers (CTC) or Cholera Treatment Units (CTU), at bigger and central or smaller and decentralized inpatient facilities, respectively (20). These CTCs or CTUs are typically set-up within existing hospital or hospital compound or health centers or health posts, and aimed at isolating and treating severe cholera patients. For moderate cholera cases, Oral Rehydration Points (ORP) are more widely serviced for early rehydration therapy and quick identification and referral of severe cases to CTC or CTU (20). The EPHI (EHNRI) guideline notes CTC and CTU must function 24 hours while ORP can be open 12 hours/day (20).

Case Management

Case management begins by assessing clinical conditions of patients visiting health facilities, followed by treatment and discharge (**Table 3**). The signs of dehydration in patients with AWD is graded based on symptoms reflecting fluid loss (20). Severity of dehydration determines different treatment options;

TABLE 2 | Activities of a Rapid Response Team (RRT) for cholera outbreak investigations.

At health facility	Review/collect data on suspected cholera patients per case definition.
	Review/collect data on patients treated for acute watery diarrhea.
	Assess health facility personnels' understanding on cholera and treatment protocols.
	Make inventory of supplies: specimen collection kits, rehydration supplies, etc.
At community	Interview patients and their families: confirm information on cases, track contracts, and identify risk factors.
	Interview any other ill persons suspected with cholera in the community.
	Interview to assess recent travel history, contacts with suspected cholera cases or/and ill persons with diarrhea, recent attendance at a funeral (and cause of death of deceased), water sources (drinking, bathing, cleaning kitchen utensils), food consumption history, occupation.
Specimens and lab tests	Collect 5–10 rectal swabs (if health facility has not performed) per outbreak/Woreda.
	Do not delay treatment of dehydrated patients to collect specimens.
	Obtain specimens before antibiotic therapy begins.
	Specimen collection within 5 days of onset of illness recommended.
	Arrange transport of rectal swabs to Regional Reference Laboratories and National Reference Laboratory at EHNRI (EPHI).
	Confirm cholera: identify strain, biotype, serotype, antibiotic sensitivity.
Data analysis	Review following information from register: name, age, sex, address, symptoms, date of onset of illness, date treated, treatment provided, treatment outcome (alive, dead, referred), specimen collection status, any risk related data, index case tracing.
	Geographical mapping of cases.
	Graph to visualize daily and accumulated cases per onset of illness.
	Analyse number of cases, deaths, attack rate (AR), case fatality rate (CFR), high risk groups, source of infection, etc.
	Analyze epi-curve to assess if an outbreak is on increase.
	Monitor Weekly Incidence Rate (WIR): i.e., high WIR as a proxy indicator of epidemic and speed of epidemic spread.
Treatment	Ensure treatment of suspected cholera or confirmed cholera patients per treatment guideline.
	Review case management at health facility: i.e., high CFR as a proxy indicator for the need to improve case management.
	Ensure availability of supplies for adequate patient treatment and specimen collection at health facility.
	Set-up a system to provide support for treatment in remotely located communities.
	Provide community health workers with Oral Rehydration Solutions (ORS).
Outbreak control	Conduct on-site control measures to prevent further transmissions linked to any identified source of infection.
	Communicate and sensitize communities and high-risk groups with simple health education messages.
Report and follow-ups	Report outbreak investigation results and actions taken.
	Follow-up surveillance visit(s).

Reconstructed based on the Guideline on Cholera Outbreak Management Ethiopia, Ethiopia Health and Nutrition Research Institute [EHNRI (now EPHI)], 2011.
RRT, Rapid Response Team; EHNRI, Ethiopia Health and Nutrition Research Institute; AR, Attack Rate; CFR, Case Fatality Rate; WIR, Weekly Incidence Rate; ORS, Oral Rehydration Solutions.

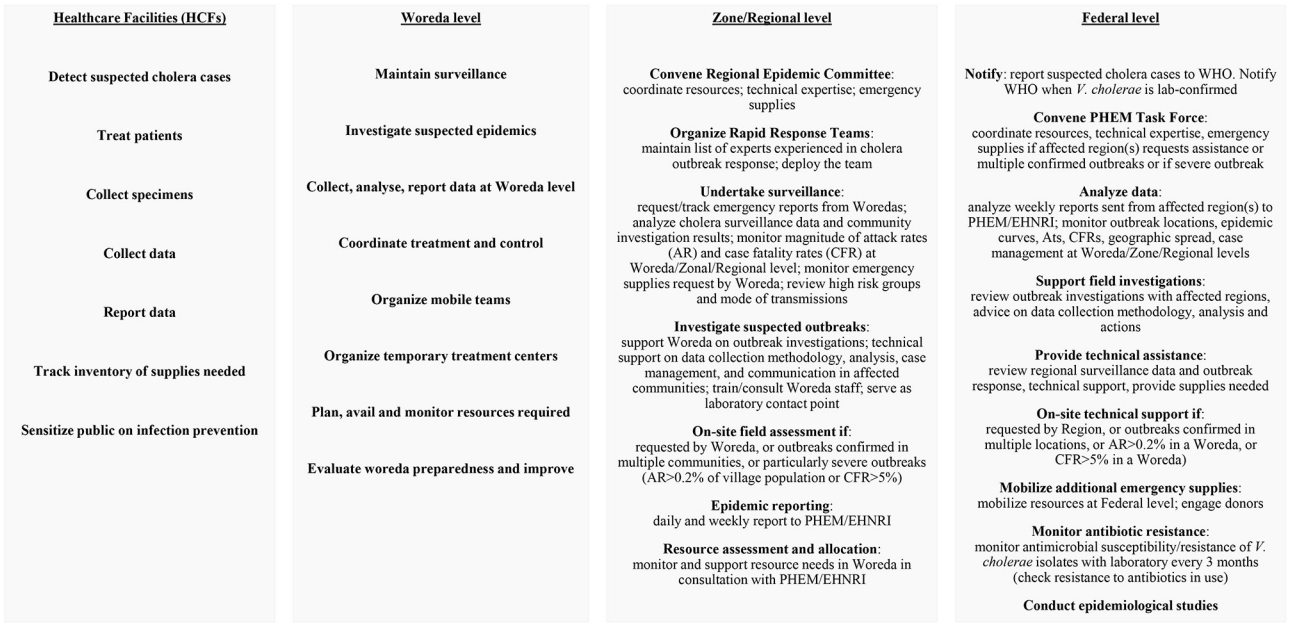
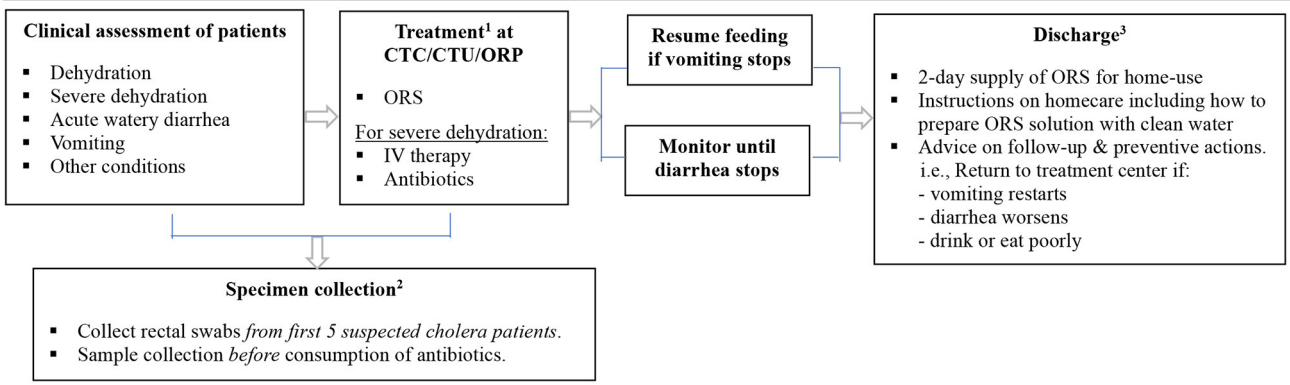


FIGURE 1 | Responsibilities in cholera detection and outbreak control.

TABLE 3 | Flow diagram of cholera case management in Ethiopia.



[1] *IV therapy for patients with severe dehydration. ORS during and after IV therapy when patient becomes able to drink. Antibiotics can reduce volume/duration of diarrhea and shorten period of infectivity. Treatment with rehydration of patients should not be delayed by specimen collection. Zinc supplementation for children with watery diarrhea including cholera is also recommended (children aged 6–59 months to receive zinc supplementation for 10 days when vomiting stops). Refer to* ***Table 4*** *for detailed treatment options for cholera case management.*

[2] *Specimen collection before antibiotics.*

[3] *Discharging patients: For hospitalized patients, transfer to recovery area for continued observation and ORS for 6 h. For patients in recovery area, discharge if no more signs of dehydration and less than three liquid stools in past 6 h.*

CT, Cholera Treatment Center; CTU, Cholera Treatment Unit; ORP, Oral Rehydration Points; ORS, Oral Rehydration Solutions; IV, Intravenous.

oral rehydration solution (ORS) for moderate dehydration, and intravenous (IV) therapy for severe dehydration (**Table 4**). Antibiotics may be also used for severely dehydrated patients, after IV rehydration, to reduce volume and duration of diarrhea and period of infectivity. Mass chemoprophylaxis is not recommended but selective chemoprophylaxis by EPHI (20) in alignment with the WHO guideline on cholera control (21). Antibiotics of choice for cholera treatment include doxycycline for adults, amoxicillin syrup for children, and erythromycin for pregnant women (20). For doxycycline resistant *V. cholerae* infection, amoxicillin and erythromycin may be used alternatively. For cholera patients with severe malnutrition, patient's weight loss can be an indicator to confirm dehydration (20). For pediatric cholera and diarrhea, zinc supplementation can be provided to reduce frequency and severity of diarrheal episodes (20). Normal feeding may be

TABLE 4 | Treatment for cholera case management.

		Acute Watery Diarrhea (AWD) with:		
		No dehydration	**Moderate dehydration** (if two or more signs, including at least one major sign)	**Severe dehydration** (if two or more signs, including at least one major sign)
Signs	Mouth/tongue	Moist	Dry	Very dry
	Thirst[1]	Drinks normally	Thirsty, drinks eagerly[3]	Drinks poorly or not able to drink[3]
	Skin pinch[2]	Goes back quickly	Goes back slowly[3]	Goes back very slowly (>2 sec) [3]
Treatment[4]		Maintain hydration (Treatment plan A) • ORS after each loose stool to maintain hydration until diarrhea stops • If patient lives far from treatment center or correct home treatment can't be guaranteed: keep under observation • Sent home with a 2-day supply of ORS with instruction on preparing ORS solution with clean water and schedule: <table><tr><td><2yr</td><td>50-100ml</td><td>1 sachet/day</td></tr><tr><td>2-9yr</td><td>100-200ml</td><td>1 sachet/day</td></tr><tr><td>≥10yr</td><td>as much as wanted</td><td>2 sachets/day</td></tr></table>• Instruct patient to return to treatment center if condition deteriorates (if repeated vomiting, number of stools increased, patient drinks or eats poorly) • If patient starts vomiting or develops abdominal distension: Ringer's Lactate 50 ml/kg over 3 h, followed by ORS after assessment of hydration status (monitor every 4 h)	ORS (Treatment plan B) • Admit to treatment center • ORS and monitor until diarrhea/vomiting stops (if patient vomits, wait 10 min, and continue slowly) • Amount of ORS required in 4 h subject to patient's weight (75 ml/kg in 4 h). If patient's weight is unknown, use age: <table><tr><td>Age</td><td>Weight</td><td>ORS solution in ml</td></tr><tr><td><4m</td><td><5kg</td><td>200-400</td></tr><tr><td>4-11m</td><td>5-7.9kg</td><td>400-600</td></tr><tr><td>12-23m</td><td>8-10.9kg</td><td>600-800</td></tr><tr><td>2-4yr</td><td>11-15.9kg</td><td>800-1200</td></tr><tr><td>5-14yr</td><td>16-29.9kg</td><td>1200-2200</td></tr><tr><td>≥15yr</td><td>≥30kg</td><td>2200-4000</td></tr></table>• During first 2 h of treatment: monitor rehydration frequently (at least every hour) • After first 4 hours of treatment: if no more signs of dehydration, follow Treatment Plan A • After first 4 h of treatment: if still signs of moderate dehydration, repeat Treatment plan B for another 4 h and reassess • At any time during treatment: if patient's symptoms deteriorate (if signs of severe dehydration, confused or disorientated, frequent/severe vomiting), immediately shift to Treatment plan C • If patient can't drink and if IV therapy not feasible at treatment center: rehydrate patient using nasogastric tube	IV, ORS, antibiotic (Treatment plan C) • Admit to treatment center • IV treatment immediately to restore normal hydration within 3–6 h: <table><tr><td>Age</td><td>First: 30ml/kg IV in:</td><td>Then: 70ml/kg IV in:</td></tr><tr><td><1yr</td><td>1 hour</td><td>5 hours</td></tr><tr><td>≥1yr</td><td>30 minutes</td><td>2.5 hours</td></tr></table>- Ringer's lactate as first choice of IV fluids - If Ringer's lactate not available, normal saline or 5% glucose in normal saline - Plain 5% glucose solution not recommended • If patient can drink, ORS 5 ml/kg/h can be also given simultaneouly with IV drip • If fluid can't be given through IV route, give ORS (20 ml/kg over 6 h) through a nasogastric tube • Assess patient's condition every 30 min during the first 2 h; then every h for next 6–12 h • Monitor pulse and respiratory rates, frequency of urine, stool, and vomiting - Regular urine output (every 3–4 h): good sign of enough fluid - Sign of increasing edema: evidence of over hydration - Sign of continued fast breathing and rapid pulse rate during rehydration: may be early signs of heart failure - Stop rehydration immediately if patient shows any of these signs • Antibiotics[5] only to patients with severe dehydration to shorten duration of illness and carriage of pathogen

Reconstructed based on the Guideline on Cholera Outbreak Management Ethiopia, Ethiopia Health and Nutrition Research Institute (EHNRI (now EPHI)), 2011.
ORS (Oral Rehydration Solution), IV (Intravenous) rehydration therapy, yr (year), m (month), h (hour).
[1] Thirst: Give fluid to patient to observe this sign.
[2] Skin pinch: Pinch abdominal skin and release to observe this sign. Notably, skin pinch may go back quickly in a severely malnourished patient such as a child with kwashiorkor even at dehydration condition. In such situation, monitoring the patient's weight is recommended to confirm dehydration.
[3] Major signs.
[4] For treatment of severely malnourished patients: ORS for moderate dehydration with no signs of shock (20ml/kg in first 2 hours at rate of 5ml/kg every 30 minutes, followed by 50ml/kg at rate of 5ml/kg/hour for up to 10 hours); and IV for severe dehydration with signs of shock (Ringer Lactate 15ml/kg/hour over 2 hours, followed by ORS 10ml/kg/hour until dehydration is corrected). Breast-feeding and therapeutic milk possible during oral rehydration.
[5] Antibiotics (per EHNRI/EPHI guideline): For only severely dehydrated cholera patients; after IV rehydration. Mass chemoprophylaxis not recommended for cholera outbreak control. Selective chemoprophylaxis (1 dose of Doxycycline) may be useful for household members sharing food and shelter with cholera patient. Doxycycline (1 dose): for adults (except pregnant women); contra-indicated in pregnant or breast-feeding women and children under 8 years of age but can be used to treat cholera as 1 dose should not have any adverse effects. Amoxicillin syrup: for children; can be used also for adults if other antibiotics not available or V. cholerae resistant to those. Erythromycin: for pregnant women; may be used if other antibiotics not available or V. cholerae resistant to those.

resumed when vomiting stops and breastfeeding for infants and young children does not need to be stopped. Cholera patient is eligible for discharge from treatment center when there are no more signs of dehydration and less than three liquid stools in the past 6 hours.

Transmission Control

The EPHI (EHNRI) guideline (20) notes disinfection of transport and houses of cholera patients as soon as cases are confirmed at health facilities. Chlorine solutions are to be used for house spraying. Household visits are also a good way to engage local populations on hygiene promotion and active case detection at community level. Distribution of water purification chemical to affected kebeles is recommended when cholera cases are reported. In shortage of water treatment supplies, it is recommended that resources are prioritized based on needs and high risks such as areas with: low latrine coverage, bordering affected kebeles, sharing common water sources with affected kebeles, located downstream from affected kebeles, camps with unsafe drinking water sources such as refugee camps, miliary, etc (20). As part of the cholera outbreak control at affected communities, local residents need to be informed of the epidemic and measures in place, emphasizing the need for early case identification, immediate referral to CTC/CTU/ORPs, and free-of-charge treatment of cholera cases (20). Communication guideline in cholera epidemics includes preventive WaSH measures at household and community levels and addressing misinformation and rumors. Several studies on past cholera outbreaks in Ethiopia highlighted the importance of prompt and effective response at the community level, involving community leaders and community-based health workers (22). Contaminated holy water sources have been often identified as one of the risk factors of cholera outbreaks in parts of the country (23). Community sensitization on behavioural change associated with WaSH such as proper hand-washing using soap, cooking of raw vegetables, consumption of safe and clean water are some of the important measures that individuals can take for protection against *V. cholerae* infection and transmission.

Use of Oral Cholera Vaccine (OCV)

Based on the World Health Assembly (WHA) Resolution 64.15 adopted in May 2011, which emphasized an integrated and comprehensive approach to cholera control including the use of OCV, the WHO in consultation with technical partners has established an OCV emergency stockpile and its implementation framework in 2013 (24, 25). Vaccines for the stockpile are procured from WHO pre-qualified manufacturers at negotiated prices. The emergency stockpile is managed by the OCV ICG for vaccine provision, based on review of the ICG request form and a reactive vaccination plan submitted by respective countries affected by ongoing cholera epidemics (25). Currently the OCV stockpile is also used in non-emergency settings for cholera prevention in cholera hotspots in endemic areas under the provision of the WHO GTFCC OCV Working Group (WG) (26, 27).

The use of OCV has increased significantly in Ethiopia since 2019 as part of the government's cholera outbreak control measures. The OCVs can be used as a reactive vaccination campaign in cholera outbreak settings or pre-emptively in cholera high-risk endemic areas to prevent potential outbreaks. With the recent cholera epidemics affecting Ethiopia with over 56,000 cases during 2015–2021 from all regions across the country, the government of Ethiopia has approached the ICG and the government of the Republic of Korea via bilateral diplomatic channel in 2019 for OCV doses to conduct reactive vaccination campaigns (28). In response to the cholera outbreaks in 2019 and 2020, the Ethiopian government has requested over 4 million doses of OCV to WHO for two rounds of vaccination campaign in 22 cholera outbreak woredas in 2020 (29). Further in 2021, around 6.8 million doses of OCV were requested and approved by the GTFCC OCV WG for use in 29 cholera hotspots in Ethiopia based on the NCP put together by the Ethiopian government (30).

SECTION 3: NATIONAL COMMITMENT FOR CHOLERA CONTROL IN ETHIOPIA

Overall, the government of Ethiopia has implemented the multi-year *Health Sector Development Plan (HSDPs)* since 1997 over the last 20 years (31–34). The Ministry of Health (MOH) has also developed and implemented the *Health Sector Transformation Plan I (HSTP-I) 2015/16-2019-20 (2008 Ethiopia Fiscal Year (EFY)-2012 EFY)*, and subsequently launched in 2020 a Joint Assessment of the National Health Strategy (JANS) to review the next phase *Health Sector Transformation Plan II (HSTP II) 2020/21-2024/25* (35). Overall, the HSTP-I has contributed to reducing morbidity and mortality of major communicable diseases in Ethiopia such as HIV, tuberculosis and malaria, but maternal and child health associated with infectious diseases still remain high (35). Further challenges in the health system in Ethiopia include high disparity in healthcare service utilisation and health outcomes among people at different geographical areas and socio-economic levels (35). Reflecting the outcome of HSTP-I, the next 5-year HSTP-II, aligned with national 10-year development plan, aims to accelerate universal health coverage (UHC), protect people from health emergencies, create Woreda transformation, make health system respond to people's needs (35). The HSTP-II includes cholera as one of the regular disease outbreaks caused by cyclical hazards along with measles and yellow fever (35).

The national guidelines specific to infectious diseases and public health emergency management in Ethiopia include the *Public Health Emergency Management (PHEM): Guidelines for Ethiopia*, EPHI (EHNRI), 2012 (36). This PHEM Guideline encompassed the International Health Regulations (IHR 2005, third edition; amendment adopted by the 67th WHA in 2014 and entered into force for all States Parties in 2016) (37) that the government of Ethiopia has also ratified. Specific to cholera control, the EPHI (EHNRI) *Guideline on Cholera Outbreak Management Ethiopia* has been developed and available since 2011 (20), providing guideline on cholera control such as: cholera surveillance (case detection and notification), outbreak investigation, outbreak response (Epidemic Committees, roles

and responsibilities of various stakeholders, case management, transmission control), cholera treatment centers (guidelines on establishing and managing CTCs), WaSH, communication, monitoring and evaluation, and cholera preparedness.

Further, the Ethiopian government has developed a multi-sectoral multi-year NCP (18) and submitted to the WHO GTFCC for Independent Review Panel (IRP) (38) in 2021. The Ethiopia NCP (Multi-Sectoral Cholera Elimination Plan in Ethiopia 2021–2028) has six main targets: (i) effective leadership and multi-sectoral coordination for cholera elimination; (ii) strengthened surveillance and laboratory capacity (laboratory culture and rapid diagnostic tests, assessment of antibiotic susceptibility of bacteria and tracking strains) at all levels for early case detection and case confirmation by 2028; (iii) cholera mortality reduction by 100% in hotspot woredas by 2028 and no local transmission in hotspot woredas; (iv) OCV vaccination with 97% coverage in hotspots (preventive) and in outbreaks (reactive); (v) increased basic water supply from 65 to 90% and sanitation and hygiene practice coverage from 6 to 80% by 2028; (vi) behavioural change in hotspot woreda population to contribute to reduction of cholera deaths by 100% (18). The hotspot analysis was conducted based on disease prevalence and persistence using the cholera hotspot mapping tool developed by the GTFCC with plans for annual revision (18).

SECTION 4: DISCUSSIONS ON CHALLENGES AND WAY FORWARD

The multi-year health sector development plans aligned with the national development plan exhibit the strong political commitment and leadership of the Ethiopian government for public health system strengthening and infectious disease management including cholera control. The NCP has been prepared by multiple government branches, including MOH, EPHI, PHEM Center, Disease and Health Surveillance and Response Directorate, Bacterial Disease surveillance and Response Case Team, Ministry of Water, Irrigation, and Electricity, National Disaster Risk Management Commission, Ethiopian Pharmaceuticals Supply Agency, Ethiopian Food and Drug Administration Authority, Regional Health bureaus, etc. in collaboration with Cholera Technical Working Group (CTWG) (18) The CTWG is composed of EPHI Public Health Emergency Management and Directorates of Infectious and Non-infectious Diseases Research, MOH Health Promotion and Disease Prevention General Directorate, as well as WHO and other external partners (18) Reflecting the WHO GTFCC guiding document on NCP development (39), the Ethiopia NCP has six pillars; leadership and coordination, WaSH, surveillance and reporting, OCV use, healthcare system strengthening, and community engagement (18). The high-level leadership from the Ethiopian government involving the Minister of Health and the Office of the Deputy Prime Minister has been instrumental in putting cholera on the national health agenda in Ethiopia and demonstrating government commitment.

In order to achieve the NCP goals in Ethiopia, improved disease surveillance, diagnostics capacity, health information reporting system, effective OCV intervention strategy, community engagement for early case detection and proper case management, and WaSH promotion is critical. Limited rapid diagnostics or laboratory diagnostics capacity particularly in remote and distanced areas from the capital and regional cities prohibits the early detection and accurate diagnostics of *V. cholerae* and other causative pathogens associated with diarrheal diseases, which may also lead to inappropriate use of antibiotics. As a result, available government records of cholera cases are often based on clinical diagnosis of suspected cholera. Improved capacity of systematic and quality surveillance and data recording in health system is needed. There are also gaps in the quality of routine health information system data in public health facilities at regional level compared to national level (40). Lack of trained personnel compromise quality of surveillance and data reporting. Regular training programs for health workers at regional, woreda, and kebele levels with committed supervision and feedback are essential (40). To enhance surveillance and laboratory capacity at all levels for early detection and case confirmation by 2028 and reducing cholera-associated mortality by 100% in cholera hotspot woredas by 2028 with no local transmission (18), sufficient structured capacity building program for health system strengthening is warranted. Further, investment in genomic surveillance and bioinformatics analysis capacity in-country will be an additional valuable asset, enabling the local public health officials and researchers to monitor the evolution and spread of *V. cholerae* and other infectious disease agents detected in Ethiopia.

Strengthened surveillance and quality reporting system will further allow the government to assess and evaluate the impact and effectiveness of vaccination when OCVs are used pre-emptively in cholera endemic hotspots or reactively in cholera outbreak settings. Improvement in the quality of population demographic census data will also contribute to better estimation of disease incidence, prevalence, mortality rates, and also vaccination coverage rates that can be one of the important variables to assess direct and indirect herd effect of OCV vaccination in cholera control. A recent review on the national Health Management Information System (HMIS) in Ethiopia exhibited discrepancies on some health indicators such as population data estimates and vaccine coverages on Ethiopia Demographic and Health Survey (EDHS) records and routine HMIS data (41). Due to the limited resources, low- and middle-income countries (LMICs) including Ethiopia often rely on surveys to gather various health sector data when routine health information system is not adequately functioning. However, such surveys are intermittently performed and do not necessarily cover all areas, resulting to lack of district-level data for better health planning. More attention to the implementation of routine data gathering and quality HMIS is important to address this gap on health sector data, and evidence-based health program interventions based on the needs identified at the sub-national levels.

An adequate OCV vaccination strategy for different cholera outbreak contexts and active case management at the community level are important to effectively prevent potential outbreaks,

control transmissions and reduce unreported deaths attributable to cholera. Several innovative OCV vaccination strategies have been introduced in different cholera epidemic and endemic countries such as the case-area targeted interventions (CATIs) (42), ring vaccination (43, 44), self-administration of the second dose of OCV (45), and integration of WaSH intervention delivery at health facilities with vaccination program (46). A recent systematic reviews and case studies on CATIs showed the approach used in 15 outbreaks in 12 countries, including Democratic Republic of Congo, Haiti, Yemen, and Zimbabwe. The analysis showed interventions varied with WaSH interventions more commonly implemented, and alert systems triggering interventions diverse from suspected cholera cases to culture confirmed cases (47). A modeling study on CATI recommended using OCV, antibiotics, and water treatment interventions at adequate radius around cases in cholera epidemic control (48). A geospatial analysis on implications of ring vaccination in Kathmandu Valley, Nepal suggested considering a ring vaccination strategy in large urban areas with recurrent seasonal outbreaks, whereby specific outbreak locations are not predictable (43). In remote resource-limited settings, a self-administration strategy for second-dose OCV delivery in urban Dhaka, Bangladesh (45) and hard-to-reach fishermen communities in Malawi (49) were demonstrated feasible. Based on the Ethiopia NCP endorsed, preemptive OCV vaccinations in endemic areas will be based on the cholera hotspot mapping. Further innovative intervention approaches in varying cholera endemic and epidemic environments in Ethiopia should be explored and their impact on cholera control evaluated. Proactive community engagement for active cholera case detection at community-level and immediate case referral for proper cholera case management is critical.

A multi-sectoral approach requires an investment in improved availability and accessibility of WaSH infrastructure nation-wide and its adequate utilisation. Currently, the national sanitation coverage in Ethiopia reached around 57%, which amounts to more than 45 million people without access to appropriate sanitation facilities (50). The water supply and latrine coverage is particularly lower among households in lower socio-economic levels and in remote areas, as well as some large crowd gathering public sites such as market places, bus stations, religious gathering sites, and even schools that can be a potential cholera transmission hotspot (18). Only around 27% water supply coverage and 35% sanitation coverage is assessed in 45 woredas that have been identified as cholera hotspots (18). There are several WaSH projects in these cholera hotspot woredas such as One-WaSH, Co-WaSH, Woreda Transformation, humanitarian WaSH cluster activities, supported by external partners such as World Bank, United Nations Children's Fund (UNICEF), United Nations Office for the Coordination of Humanitarian Affairs (OCHA), bilateral government donors, and other non-governmental organizations (NGOs).[18] The WaSH pillar constitutes nearly 55% of USD404 million, the total budget for implementing the Ethiopian NCP in the next 8 years (18) The transparent and efficient management of resources, including allocation and use of available resources, should be ensured by the Ethiopia government-led coordination of health sector for aid effectiveness. Accountable monitoring of financing and tracking of indicators are important for the success of national cholera control and other infectious disease control and prevention broadly.

Going forward, a comprehensive monitoring of the actual practice related to cholera case detection, healthcare facility and laboratory capacities on cholera surveillance, diagnostics and reporting, tracking of OCV usage and various WaSH projects, in comparison to the available national guidelines, will provide a more robust baseline to track NCP progress and assess impact of interventions. Lessons learnt from NCP development and roll-out in Ethiopia may serve as a reference for countries with similar public health agenda. Managing cross-border transmission of cholera and other infectious diseases especially with neighboring countries that share common water sources, corridors of transportation, and frequent movement of people remains an important area for multi-stakeholder policy dialogues and joint health research. Climate change may further pose past trends of cholera seasonality less predictable, which may lead to cholera and other infectious disease outbreak response and preparedness more challenging. Further research and public health interventions to address the knowledge and health service gaps concerning cholera in Ethiopia, as well as the trend and impact of climate change and other risk factors associated with infectious diseases are warranted. A systematic and robust monitoring and evaluation program is essential for the successful execution of multi-sectoral NCP roll-out in Ethiopia. Capacity building in cholera surveillance and laboratory diagnostics, health information reporting system, WaSH access and utilisation, early case detection and case management, effective OCV vaccination strategies, and community awareness on disease prevention at all levels in Ethiopia should be guaranteed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SP: conceptualization and original writing. SP, YJ, SK, AG, DH, BY, ME, MG, and MT: review and editing. All authors contributed to the article and approved the submitted version.

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Influencing Factors Related to Female Sports Participation Under the Implementation of Chinese Government Interventions: An Analysis Based on the China Family Panel Studies

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Objectives: Regular sports participation is a gendered phenomenon in China. Women have reported much higher constraints than men on time, partner, psychology, knowledge, and interest. This study explores personal, family, lifestyle, and health factors associated with sports participation.

Study Design: This study is a cross-sectional study.

Methods: Data were collected from the national reprehensive China Family Panel Studies (CFPS) database (2018) to analyze personal information, family background, lifestyle, and health in relation to women's sports participation. Multiple classification logistic regression was used to quantify the association between independent variables and sports time.

Results: Women with high personal income and education, who were unmarried, in faster economic development areas have more awareness and more time for sports participation. Women who were overweight and self-rated as unattractive spent less time on sports participation. Women with a small family population and no children have more time for sports participation. Less time on the internet and moderate sleep contribute to active sports participation. Women with chronic diseases and high medical costs are less likely to participate in sports.

Conclusions: Negative body aesthetic perception, the burden of family environment, modernization of lifestyle, and the normalization of sub-health are essential factors affecting women's sports participation. The government should understand the inner and outer barriers to women's participation in sports, develop policies and regulations to protect and support women's sports participation, and guide and monitor the effective implementation of women's sports activities.

Keywords: China, influencing factors, physical activity, women, government

INTRODUCTION

The World Health Organization reached a consensus that health is a state of physical, mental, and social wellbeing, which indicates that the healthy development of the body is the cornerstone of everything (1). Increasing sports participation in regular physical activity to promote health is a national health priority for many developing nations (2). It is one of the effective ways to improve the health level of all the residents (3–5). Most Chinese remain inactive despite the known health benefits, and sports participation is a gendered phenomenon in China. Women have reported much higher constraints than men in terms of time, partners, psychology, knowledge, and interest (6–9).

Sedentary behavior describes the absence of sports participation. Suppose the body rapidly maladapts to insufficient physical activity and continues, resulting in substantial decreases in total and quality years of life. In that case, a sedentary lifestyle is one of the primary causes of global deaths, accounting for 5 million each year (10, 11). Therefore, reducing sedentary behavior among women and promoting sports participation may be essential strategies for reducing out-of-pocket health care expenditure in China (12).

To further develop the cause of national fitness, the Chinese government formulated a national fitness plan in two stages, first between 2011 and 2015, followed by another from 2016 to 2020, and the plan will be a "national business card." According to the plan, by 2020, a significant increase is expected in the number of people taking part in sports, meaning people's physical quality will steadily improve. The number of people who participate in sports once a week or more can reach 700 million, and the number of people who regularly participate in sports will reach 435 million. After NFP (national fitness plan) implementation, the sports participation rate increased. Sports programs continue to enrich covering urban and rural areas. A relatively sound public service system for national fitness has improved sports participation, particularly female sports participation. In addition, the "Health China 2030" plan was implemented in 2016, aiming to build a healthy China over the next 15 years, integrating health into national policy and elevating it to the level of a national priority development strategy. Women's sports participation is an essential part of constructing a healthy China. The outline points out that strengthening health services for key populations and paying attention to the physical health of young people, women, the elderly, and other special groups. Policy encouraging women to undertake sport-related activities is more common than before. After implementing these programs, more women participated in activities such as marathons, bodybuilding, and outdoor sports.

The current study analyzes the factors that influence women's sports participation in China based on the China Family Panel Studies (CFPS) database. The study provides a guide for improving the overall level of women's health in China on a theoretical basis and shares opinions for constructing a healthy China.

STATEMENT OF THE STUDY

Many factors (economic, educational background, cultural impact, and domestic roles) influence women's sports participation (13, 14). The cultural background of different countries can impact women's participation in sports (15). As Laar et al. have observed, "Mass Media" and 'Religious and Cultural' factors are the most influential reasons for women's participation in sports. Other studies have highlighted a lack of knowledge, overcrowding, lack of time, long-distance, and family and financial problems as the most significant constraints women face in sports participation (16–18). Enne (19), Rosenfeld (20), and Downward et al. (21) have investigated socioeconomic, lifestyle, motivational factors, as well as the availability of sports facilities and government support related to female sports participation (20–22). Hanlon believed that a lack of professional sports knowledge significantly affects Malaysian women's sports participation (23). Sociocultural norms, family constraints, and lack of awareness about the benefits of sports strongly influenced physical activity among the different ages of US South Asian women (24).

Rodney conducted a systematic integrative literature review to identify factors affecting physical activity among African American women. These factors were classified as intrapersonal, interpersonal, and environmental (25). Studies have found that married individuals spend less time exercising and engaging in moderate to vigorous exercise than unmarried individuals. A decrease in physical activity time is more pronounced among married women than married men (26–28). In China, compared with rural areas, female participants from urban areas tended to have more leisure time for physical activity and less vigorous-intensity physical activity (29). In addition, fitness-health, enjoyment-interest, and appearance were the most critical motives, and lack of time, resources, skills, and family or friend support were the most pressing barriers to participation. Higher-income was a stronger predictor of physical activity participation in middle-aged women (16). Jing found that ill health, low energy, and lack of self-discipline affect women's physical activity (9). Choi et al. indicated that some personal and environmental factors were related to participation in physical activity. However, there is a lack of primary studies that build up organized evidence. Therefore, more studies with a prospective design should be conducted to understand the potential causes of physical activity (30). However, these studies only explore the relationship between a single variable or a few variables and female sports participation, which lacks integrity and hierarchy. The scope of research objects and the data need to be dated.

METHODS

Data Sources

We used the 2018 CFPS database, a large-scale and nationally representative survey by the Chinese Social Science Survey Center of Peking University (31). CFPS uses multi-stage sequential sampling with stratified indicators. The baseline sample covers 25 provinces/municipalities/autonomous regions

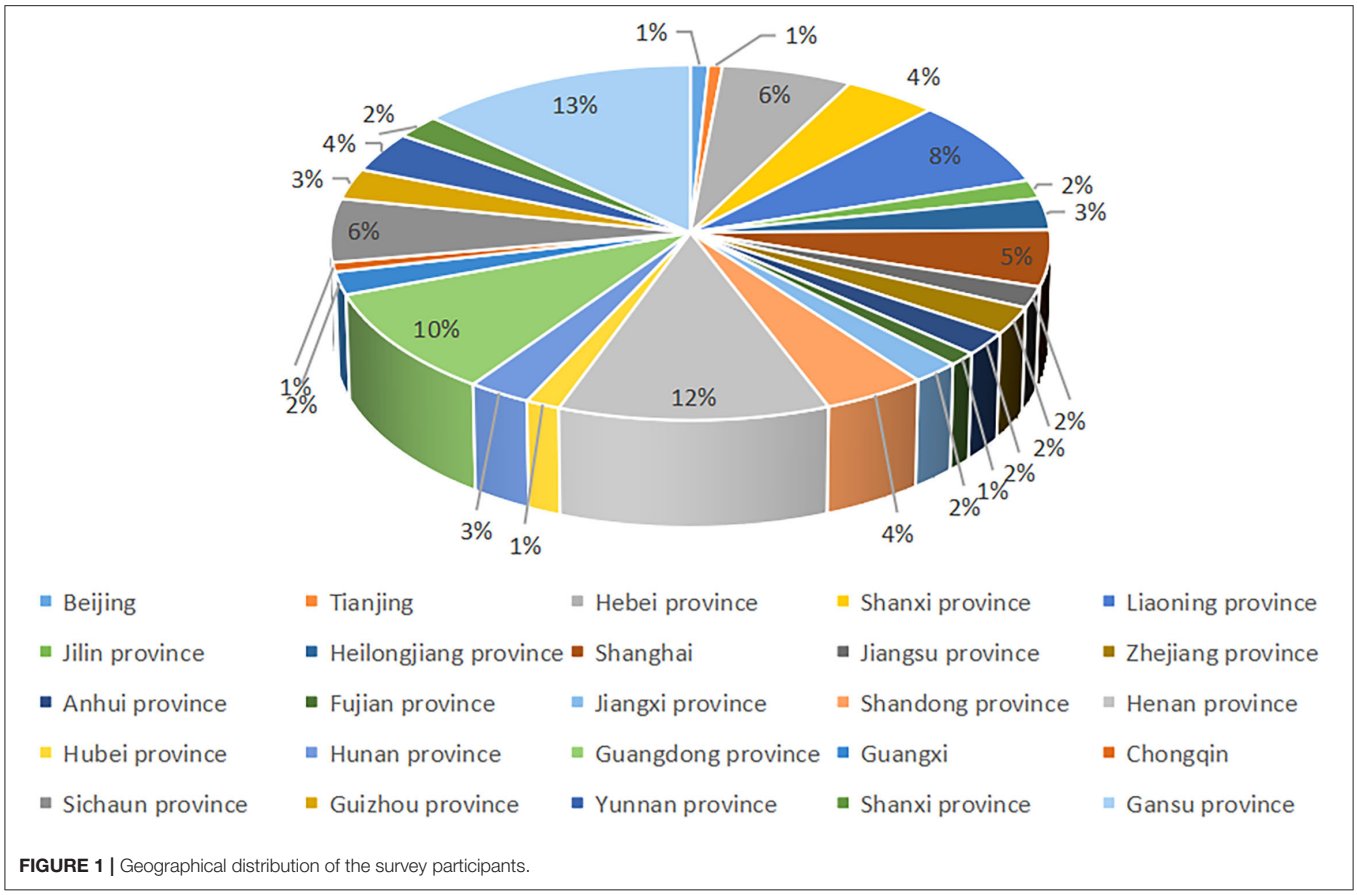

FIGURE 1 | Geographical distribution of the survey participants.

(excluding Xinjiang, Tibet, Qinghai, Inner Mongolia, Ningxia, Hainan and Hong Kong, Macao, and Taiwan), representing 95% of China's population. The total sample size for 2018 was 14,241 households with 32,669 individuals. CFPS data can therefore be viewed as a nationally representative sample (**Figure 1**).

Women aged 16–59 were the research object (studies have proved that the elderly group over 60 years old is an active group of physical activity, so there is no specific discussion) (32). We focused on the impact of their characteristics, family environment, work background, lifestyle, and urbanization, while mainly focusing on health status during PA time. Therefore, we omitted all-male data, and 2,096 females who were not in the age group of 16–59 years, 3,338 observations with missing values were also deleted. A sample of 10,938 was obtained, and the omitting rate was 20.4%. I have employed imputation methods to compensate for missing values. Each missing value is assigned a simulated value according to the distribution of missing data, which can be seen in **Supplementary Table 1**.

SPECIFICATION OF VARIABLES AND MODEL

Variables Specification

The dependent and independent variables are in **Table 1**.

Model Specification

The fitting degree test of multiple logistic regression models is based on fitting information, appropriate degree, and pseudo R^2. When independent variables are not introduced in the model, the 2-fold log fit is 28227.301, reduced to 23557.214, a degree of freedom of 153, $p < 0.01$. The whole model is significant, and both the Pearson and the deviation were significantly >10%. The pseudo-deterministic coefficients for Cox and Snell, Nagelkerke, and McFadden are 0.148,0.176,0.165, respectively. These indicators show that the model fits well and fulfills the required standard (33). Therefore, it is appropriate to use the multinomial logistic regression model. The interpretation of the model reached 53.0%. A multiple logistic regression model of influencing factors of women's sports time consists of three models: model 1, model 2, and model 3. Model 1 is a comparison between level 1 and level 4. Model 2 is a comparison between level 2 and level 4, and model 3 is a comparison between level 3 and level 4. The specification of dependent and independent variables are in **Supplementary Table 2**.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA), significance level set at $p < 0.05$.

TABLE 1 | Variable description of female participants ($N = 10,938$).

		Variables	Description	*N*	%
Dependent variables	Sports participation	Sports time	Never	2,202	20.13
			0–90 min	3,234	29.57
			90–180 min	3,092	28.27
			More than 180 min	2,410	22.03
	Body image	BMI	Low weight	1,329	12.2
			Overweight	2,788	25.5
			Obesity	930	8.5
			Normal	5,891	53.9
		Appearance	well	1,386	12.7
			normal	2,627	24
			not well	6,925	63.3
	Personal information	Age	16–29	2,790	25.5
			30–39	2,466	22.5
			40–49	2,755	25.2
			50–59	2,927	26.8
		Location	east	4,099	36.5
			central	3,538	32.3
			west	3,301	30.2
		Education level	Unschooled	2,989	27.3
			Elementary School	2,320	21.2
			High School	2,408	22
			Undergraduate	1,709	15.6
			Postgraduate	1,512	13.8
Independent variables		Household register	Urban	5,673	51.9
			Countryside	5,265	48.1
		Marital status	Married	6,265	52.3
			Unmarried	4,673	47.7
		Income	<1,000	7,396	67.6
			1,000–3,000	2,730	25
			>3,000	1,297	11.9
		Children	Yes	5,769	52.7
			No	5,169	47.3
	Family environment	Family population	>5	3,954	36.1
			3–5	4,182	38.2
			<3	2,792	25.5
		Frequency of caring for father	Seldom	8,951	81.8
			Sometime	1,123	10.3
			Always	864	7.9
		Frequency of caring for mother	Seldom	8,398	76.8
			Sometime	1,513	13.8
			Always	1,029	9.4
		Usage time of Internet	<1 h/day	2,704	24.7
			1–2 h/day	5,231	47.8
			2–3 h/day	1,438	13.1
			>3 h/day	1,565	14.3
	Lifestyle	Sleeping time	<6 h	4,017	36.7
			>8 h	1,371	12.5
			6–8 h	5,550	50.7
		Smoke	Yes	245	2.2
			No	10,693	97.8
		Drinking	Yes	299	2.7
			No	10,639	97.3

(Continued)

TABLE 1 | Continued

	Variables	Description	*N*	%
Health condition	Health level	Unhealthy	2,898	26.5
		Healthy	8,040	73.5
	Chronic	Yes	2,202	20.1
		No	8,736	79.9
	Medical insurance	Yes	9,924	90.7
		No	1,014	9.3
	Medical expenses	>1,000	3,322	30.4
		500–1,000	3,434	31.4
		1–500	4,182	38.2

TABLE 2 | Multiple Logistic Regression models of contributing factors of female participation in physical activity (personal information).

Independent variable		Model 1		Model 2		Model 3	
		RC (SEM)	RRR (95%CI)	RC (SEM)	RRR (95%CI)	RC (SEM)	RRR (95%CI)
Age	16–29 years old	1.15** (0.14)	1.31 (1.20–1.42)	0.89** (0.12)	1.78 (1.74–1.83)	0.71 (0.18)	1.73 (1.53–1.97)
	30–39 years old	0.75** (0.12)	1.58 (1.53–1.63)	1.25** (0.10)	1.67 (1.61–1.73)	0.72 (0.16)	0.68 (0.59–0.77)
	40–49 years old	0.26** (0.09)	1.22 (1.12–1.33)	0.31** (0.08)	1.78 (1.74–1.82)	0.41 (0.12)	1.11 (0.96–1.28)
	50–59 years old	Referent	–	Referent	–	Referent	–
Location	East	−0.34** (0.07)	0.85 (0.72–0.98)	0.12 (0.07)	1.14 (1.09–1.19)	−0.16 (0.10)	1.65 (1.46–1.87)
	Central	−0.24** (0.07)	0.98 (0.91–1.05)	0.15 (0.07)	1.34 (1.29–1.39)	−0.03 (0.10)	0.65 (0.57–0.73)
	West	Referent	–	Referent	–	Referent	–
Education level	Unschooled	0.67** (0.19)	1.70 (1.58–1.84)	0.31** (0.08)	1.70 (1.61–1.79)	0.43** (0.12)	1.52 (1.46–1.58)
	Elementary School	0.56** (0.18)	1.53 (1.48–1.58)	0.40** (0.13)	1.66 (1.60–1.72)	0.38** (0.12)	1.47 (1.14–1,89)
	High School	0.27** (0.12)	1.09 (0.97–1.23)	0.21** (0.14)	1.23 (1.04–1.46)	0.25** (0.17)	1.82 (1.56–2.12)
	Undergraduate	0.28** (0.20)	1.07 (0.91–1.25)	0.005 (0.15)	0.84 (0.76–0.92)	−0.08 (0.19)	1.62 (1.32–1.97)
	Postgraduate	Referent	–	Referent	–	Referent	–
Household register	Urban	0.17* (0.07)	1.18 (1.09–1.27)	−0.60** (0.06)	0.67 (0.64–0.70)	−0.23** (0.11)	0.79 (0.65–0.97)
	Rural	Referent	–	Referent	–	Referent	–
Marital status	Married	1.32** (0.15)	2.09 (1.57–2.61)	0.98** (0.16)	2.66 (1.94–3.64)	1.15** (0.12)	2.02 (1.76–2.33)
	Unmarried	Referent	–	Referent	–	Referent	–
Income	<1,000	0.59** (0.12)	1.55 (1.43–1.70)	0.57** (0.11)	1.66 (1.54–1.81)	1.59** (1.12)	1.55 (1.42–1.72)
	Between 1,000 and 3,000	0.23** (0.14)	1.81 (1.64–2.04)	0.21** (0.11)	1.86 (1.81–0.91)	0.09 (0.14)	1.41 (1.22–1.62)
	More than 3,000	Referent	–	Referent	–	Referent	–
BMI	Low weight	0.04 (0.14)	1.32 (1.17–1.49)	0.04 (0.10)	0.84 (0.78–0.91)	0.04 (0.14)	1.16 (0.94–1.42)
	Overweight	0.09** (0.08)	1.10 (0.94–1.27)	−0.13 (0.09)	1.31 (1.26–1.37)	−0.05 (0.12)	0.86 (0.76–0.98)
	Obesity	0.59** (0.13)	1.16 (1.06–1.27)	0.81** (0.11)	1.77 (1.73–1.81)	0.25* (0.13)	1.12 (0.97–1.30)
	Normal	Referent	–	Referent	–	Referent	–
Appearance	Not well	1.17** (0.09)	1.52 (1.36–1.70)	1.60** (0.07)	1.19 (1.13–1.27)	0.17 (0.12)	0.41 (0.29–0.57)
	Normal	0.18 (0.06)	1.08 (0.98–1.20)	0.23 (0.04)	0.66 (0.62–0.70)	0.08 (0.05)	1.59 (1.39–1.82)
	well	Referent	–	Referent	–	Referent	–

*RC, regression coefficient; RRR, Relative Risk ratio; BMI, body mass index, *p < 0.05, **p <0 .01 for the referent.*

RESULTS

Personal Information Contributes to Independent Variables of Women's PA Time

The higher the education, the longer sports participation. Unmarried women spend more time on sports than married women. The higher the income, the more women participate in sports. Compared with women who do not participate in sports and who spend more than 180 min on sports, the age of 16–29 [1.31,95% (1.20–1.41)], 30–39 [1.58, 95% (1.53–1.63)] and 40–49 [1.22, 95% (1.53–1.63)] were 1.31, 1.58 and 1.22 times as inactive as those aged 50–59. Women in the west were 1.18 times more likely to not participate in sports than those in the East [0.85,95% (0.71–0.98)]. Urban women [1.18, 95% (1.09–1.27)] are 1.18 times more likely to not participate in sports than rural women. Obese women [1.16, 95% (1.06–1.27)] were 1.16 times more likely

TABLE 3 | Multiple Logistic Regression models of contributing factors of female participation in physical activity (family background).

Independent variable		Model 1		Model 2		Model 3	
		RC (SEM)	RRR (95%CI)	RC (SEM)	RRR (95%CI)	RC (SEM)	RRR (OR95%CI)
Children	Yes	0.19** (0.08)	0.88 (0.81–0.95)	0.21** (0.07)	1.49 (1.42–1.56)	−0.04 (0.10)	0.67 (0.59–0.75)
	No	Referent	–	Referent	–	Referent	–
Family population	More than 5	0.62** (0.10)	1.95 (1.87–2.04)	0.17* (0.07)	1.44 (1.39–1.50)	0.27 (0.13)	1.30 (1.14–1.47)
	Between 3 and 5	0.32** (0.08)	1.65 (1.61–1.70)	0.12 (0.09)	0.75 (0.71–0.79)	0.12 (0.11)	0.81 (0.72–0.91)
	Less than 3	Referent	–	Referent	–	Referent	–
Frequency of caring for father	Seldom	0.16 (0.15)	0.72 (0.65–0.79)	0.33* (0.13)	1.50 (1.39–1.61)	0.05 (0.18)	0.80 (0.68–0.94)
	Sometime	−0.23 (0.18)	1.42 (1.26–1.60)	−0.23 (0.16)	0.65 (0.59–0.72)	−0.45 (0.23)	1.08 (0.86–1.34)
	Always	Referent	–	Referent	–	Referent	–
Frequency of caring for mother	Seldom	0.34** (0.13)	0.80 (0.73–0.87)	0.14* (0.11)	1.40 (1.32–1.49)	0.10 (0.16)	0.76 (0.66–0.87)
	Sometime	0.30 (0.16)	1.34 (1.20–1.48)	−0.37 (0.14)	0.69 (0.64–0.75)	0.10 (0.19)	1.23 (1.04–1.47)
	Always	Referent	–	Referent	–	Referent	–

RC, Regression coefficient; RRR, Relative Risk ratio, $^{*}p < 0.05$, $^{**}p < 0.01$ for the referent.

to not participate in sports than normal women. Unattractive women [1.52,95% (1.36–1.70)] were 1.52 times more likely to be inactive than attractive women (**Table 2**). The sports time was 0-90min compared with more than 180 min. The age ranges 16–29 [1.78, 95% (1.74–1.83)], 30–39 [1.67, 95% (1.61–1.73) and 40–49 [1.78, 95% (1.74–1.82)] had 0–90 min sports times of 1.78, 1.67, and 1.78 times than those aged 50–59. Urban women had a sports time of between 0 and 90 min, which was 1.49 times higher than women who lived in rural areas [0.67, 95% (0.64–0.70)]. Obese women [1.77, 95% (1.73–1.81)] had a sports time of between 0 and 90 min, which was 1.77 times more than normal (**Table 2**).

Family Background Contributes to Independent Variables of Women's PA Time

Women without children were 1.136 times more likely to not participate in sports than women with children [0.88, 95% (0.81–0.95)], but women with children [1.49,95% (1.42–1.56)] were 1.49 times more likely to exercise for 0–90 min than women with children (**Table 3**). Women with families of more than five were more likely to be inactive than women with families of less than three. Women who never took care of their fathers [1.50, 95% (1.39–1.61)] had 0–90 min sports time and were 1.5 times more likely to undertake exercise than women who took care of their fathers all the time. Women who cared for their mothers were more likely to participate in sports than women who never cared for their mothers [0.80, 95% (0.73–0.87)] (**Table 3**).

Lifestyle and Health Conditions Contributing Independent Variables of Women's PA Time

For sports participation times between 90 and 180 min, women who used the internet for <1 h [1.39, 95% (1.21–1.60)], 1–2 h [1.45, 95% (1.36–1.55)], and 2–3 h [1.63, 95% (1.56–1.71)] were 1.39, 1.45, and 1.64 times more likely to exercise than women who used the internet for 3 h a day. Women who slept less than 6 hours [1.39, 95% (1.24–1.64)] and more than 8 hours [1.74,95% ([1.53–1.95)] and were 1.39 and 1.74 times more likely to exercise than women who slept between 6–8 h. Women who were unhealthy, with chronic diseases, and who paid high medical expenses spent less time playing sports than healthy women (**Table 4**).

DISCUSSION

This study explored the associations of women's sports participation with personal-related, family environment-related, and lifestyle-related factors in 10,938 Chinese women aged between 16 and 59 years old. We found that women aged 50–59 participate in sports for longer because they are less competitive at work and have more leisure time toward retirement. Other age groups are busy with school, work and family. This finding was similar to those in research by Santos (34). Due to urbanization factors, western China's economic and cultural development lags behind central China's, and there is insufficient awareness of female sports participation in the west. Meanwhile, higher education gives individuals more spare time for exercise. As some studies have shown, the higher the education level, the more positive the attitude toward exercise, and the more regular the sports participation (35, 36). Studies have found that married women spend less time on sports than unmarried women. Because married women are family-oriented and devote less time to leisure (37), especially in married women than men (26–28). However, married women are more likely to spend 0–90 min exercising with their children and other family members. A higher income level may serve as a marker for more discretionary time or resources that enable Chinese women to engage in higher levels of sports. This finding is consistent with previous studies among women in general (14).

A survey in Chinese provinces found that 34% of adults between the ages of 20 and 69 are overweight, 18.9% are overweight, and 2.9% of people in China are obese (38). Significantly, physical inactivity was associated with

TABLE 4 | Multiple Logistic Regression models of contributing factors of female participation in physical activity (lifestyle and health condition).

Independent variable		Model 1		Model 2		Model 3	
		RC (SEM)	RRR (95%CI)	RC (SEM)	RRR (95%CI)	RC (SEM)	RRR (95%CI)
Usage time of internet	< 1 h a day	−0.26 (0.14)	1.50 (1.37–1.63)	0.07 (0.12)	0.70 (0.65–0.74)	−0.49** (0.17)	1.39 (1.21–1.60)
	Between 1 and 2 h a day	−0.08 (0.13)	0.62 (0.58–0.67)	0.15 (0.11)	0.98 (0.91–0.15)	−0.39* (0.16)	1.45 (1.36–1.55)
	Between 2 and 3 h a day	−0.25 (0.16)	1.27 (1.11–1.44)	−0.11 (0.14)	0.69 (0.63–0.76)	−0.53** (0.18)	1.63 (1.56–1.71)
	More than 3 h a day	Referent	–	Referent	–	Referent	–
Sleeping time	<6 h	0.33** (0.078)	1.39 (1.24–1.64)	−0.02 (0.10)	0.75 (0.72–0.79)	−0.09 (0.14)	1.00 (0.88–1.14)
	More than 8 h	0.55** (0.11)	1.74 (1.53–1.95)	0.22* (0.09)	1.39 (1.33–1.45)	−0.09 (0.13)	1.00 (0.88–1.13)
	Between 6 and 8 h	Referent	–	Referent	–	Referent	–
Smoke	Yes	−0.43 (0.26)	0.85 (0.62–1.18)	0.06 (0.18)	0.99 (0.85–1.14)	−0.64 (0.35)	0.60 (0.33–1.10)
	No	Referent	–	Referent	–	Referent	–
Drinking	Yes	−0.12 (0.22)	1.33 (0.92–1.92)	−0.32 (0.17)	0.92 (0.80–1.05)	−0.18 (0.26)	0.93 (0.61–1.42)
	No	Referent	–	Referent	–	Referent	–
Health level	Unhealthy	0.39** (0.08)	1.58 (1.37–1.79)	0.23 (0.07)	1.15 (1.09–1.21)	0.10 (0.11)	1.28 (1.09–1.49)
	Healthy	Referent	–	Referent	–	Referent	–
Chronic diseases	Yes	2.38** (0.11)	4.65 (4.35–4.96)	0.49** (0.11)	0.47 (0.43–0.51)	0.78** (0.15)	0.66 (0.54–0.80)
	No	Referent	–	Referent	–	Referent	–
Medical insurance	Yes	0.10 (0.13)	1.16 (1.00–1.34)	0.03 (0.10)	1.02 (0.95–1.09)	0.02 (0.14)	0.83 (0.68–1.01)
	No	Referent	–	Referent	–	Referent	–
Medical expenses	More than 1,000	0.42** (0.09)	0.96 (0.88–1.04)	0.07 (0.07)	0.92 (0.88–0.96)	−0.08 (0.10)	1.15 (1.01–1.31)
	Between 500 and 1,000	0.37** (0.09)	0.81 (0.75–0.87)	0.41** (0.07)	1.32 (1.27–1.37)	0.09 (0.10)	0.78 (0.69–0.89)
	Between 1 and 500	Referent	–	Referent	–	Referent	–

*RC, Regression coefficient; RRR, Relative Risk ratio, *$p < 0.05$, **$p < 0.01$ for the referent.*

being overweight/obesity (39). Body mass index and waist circumference have increased considerably in women over 20 years. In 2018, overweight and obese women had less time for sports participation. Sports are often considered an effective way to reduce fat and improve body shape. Even though overweight and obese people should participate, overweight and obese women are sometimes unwilling to participate in sports (40, 41). They tend to associate this experience with low self-esteem, embarrassment, and feelings of vulnerability (42, 43), meaning individuals are likely to give up or avoid participation in sports due to psychological stress and anxiety. A systematic integrative literature review to identify factors to sports participation classified the elements as intrapersonal, interpersonal, and environmental (25). Women with poor physical appearance have anxiety when participating in sports, which can take the form of concern or fear related to being negatively evaluated by others in situations where the physical appearance of an individual can be assessed by others.

We found that the family population is also an essential aspect of the family environment. Our study indicates families of less than three persons are more likely to participate in sports. The women need to take care of all family member's needs, and women with small families spend their time undertaking low-cost leisure activities such as sports in China. These findings are consistent with those of a previous study (44). Women who regularly care for their mothers have time for participation in sports since women who care for their mothers also insisted on accompanying them to participate in appropriate sports activities. This is the same need for women in many developing countries to have family responsibilities and care ethics (45).

Thirdly, we found that moderate sleep helps with active participation in sports. Being addicted to the internet, playing games, watching TV, and other bad life habits significantly reduce women's sports participation time. There was a negative association between screen time and sports participation (46, 47). Moderate sleep is more helpful for women to be active in sports participation than low and high sleeping time (48). This is consistent with existing studies, which indicate that inadequate sleep and excessive sleep have adverse effects on women's sports participation time (49).

Fourth, we also found that physical inactivity increases the health risks and disease burden in China (50). Health level, chronic diseases, and medical expenditure have significant effects on women's participation in sports. Unhealthy women have a higher probability of not participating in sports than healthy women. Individuals with limited exercise capacity due to the disease were less likely to participate in sports, especially for long periods. This study does not support the significant role of health insurance in sports participation, probably because China's current health insurance system is relatively complete, with broad coverage and many types, and the effect of having or not having health insurance on sports participation is not significant. This study indicates that women with chronic diseases have less will to participate in sports, and increasing sports participation could reduce total medical costs to some extent (51). Sports participation leads to metabolic disorders,

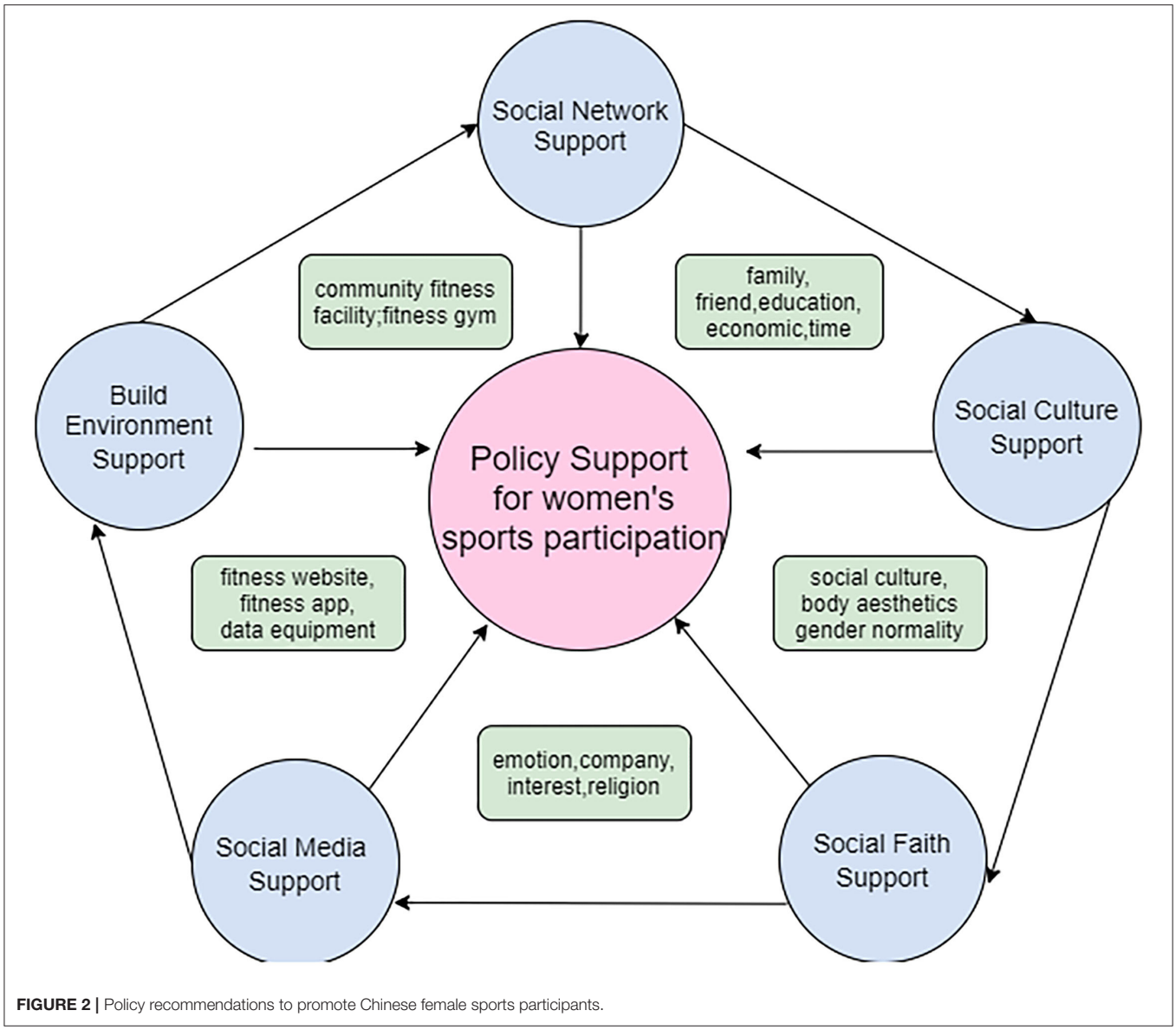

FIGURE 2 | Policy recommendations to promote Chinese female sports participants.

obesity, type 2 diabetes, and other diseases. Studying the correlates of sports time is an essential prerequisite for designing relevant policies and effective programs. The current study can give a fresh understanding of Chinese women's physical activity participation rate and barriers. It will help promote the health of women and the next generation and ultimately contribute to realizing the "Healthy China" strategy. The government should understand the inner and outer barriers to women's participation in sports, develop policies and regulations to protect and support women's sports participation, and guide and monitor the implementation and effective implementation of women's sports activities (**Figure 2**).

There were some limitations to this study. The first is that no information was collected on the type of sports activities undertaken by women. Secondly, some data were self-reported, making them prone to reporting bias, which may add some measurement error. Another important factor is the lack of discussion on the impact of women's work environment (working hours, type of work, length of work) on sports participation time.

CONCLUSION

Women with high personal income and education, who are unmarried, in faster economic development areas have more vital awareness and more time for sports participation. Women who are overweight and unattractive have anxiety about sports participation. Women with a small family population and no children have more time for sports participation. Spending less time on the internet and having moderate sleep contribute to active sports participation. Chronic diseases and high medical expenses give women no time for sports participation.

Overall, negative body aesthetic perception, the duality of family and social work, the modernization of lifestyle, and the normalization of sub-health are essential factors affecting women's sports participation.

The government should develop policies and regulations to protect and support women's sports participation in the following areas, and guide and monitor the effective implementation of women's sports activities. Firstly, developing social network support policies to increase solid relational support, such as family, friends, emotional support, time, and economic support. Secondly, developing social environment support policies to alleviate social gender norms and socio-cultural restrictions in sports, could help women establish better body aesthetic concepts, and enhance body confidence through physical exercise. Improving the safety of fitness communities, transportation accessibility convenience, and the comprehensiveness of sports facilities could also increase women's willingness to participate in sports. Finally, improving social media support to increase the positive impact of social media programs through fitness websites, fitness APPs, and data monitoring software could also help enhance women's participation in sports.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

PF had the idea for the article, drafted the article, wrote the sections of the article and analyzed the data, and conducted and reported the work described in the article. LS participated in the discussions, organized the planning, and continued to write and revised the article. YL checked supplementary materials. PF and SS are responsible for the overall content as guarantors. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Evaluation of the validity of the physical exercise peer support questionnaire for college students

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Peer support for physical exercise is defined as behaviors such as mutual or one-way provision of material help and/or emotional care and companionship between peers in the physical environment and/or physical behavior. The assessment of peer support is complex and based on reasoning. Trustworthy assessment processes need to provide sufficient evidence of validity. The purpose of this study was to organize, collect, and use Kane's validity framework to provide validity evidence for the identification of peer support for physical exercise among college students. The article describes the experience of using the framework in this study, considers data related to the four inferences (scoring, generalization, extrapolation, and implication) that emerge from the assessment process. The findings of the study are then interpreted through the four inferences to determine whether this evidence supports the purpose of this study. Based on Kane's framework to explain the validity process of this study, the study concludes that the evidence in terms of scoring, generalization, extrapolation, and implication supports the use of the PEPSQ for the identification of physical exercise peer support among college students.

KEYWORDS

college students, physical exercise, peer support, validity, PEPSQ

Introduction

The university stage is an important period of individual transition and development, and an important stage of health reserve in adulthood. College students are the future force of national construction, and the physical health of college students has far-reaching significance for national quality improvement and population structure optimization. With the continuous expansion of the enrollment scale of Chinese higher education institutions, the number of college students continues to increase, but the physical health level of Chinese college students shows a gradual downward trend (1, 2). The Report on the Development of Youth Sports in China (2015) points out that the performance of Chinese college students in various physical fitness tests is still at

a low level, and the test results of certain items are sometimes inferior to those of secondary school students (3). In 2020, the Chinese Ministry of Education conducted physical fitness review tests on 1.15 million school students. The results of the test showed that about 30% of college students failed the physical fitness test, the highest percentage among all academic levels (4). Scholars point out that effective health education guidance is needed to improve the physical health level of college students, and the physical health level of college students can be improved by encouraging them to actively participate in physical exercise (5). Although the physical and mental health effects of physical exercise have been widely recognized by the public, the lack of participation in physical exercise among college students is still a common phenomenon 2015 physical exercise survey data of college students in 23 countries around the world showed that the proportion of insufficient physical exercise among college students was as high as 41.4%. Among them, the percentage of insufficient physical exercise among Chinese college students was 37.0% (6). Therefore, finding the key elements that potentially affect college students' participation in physical exercise is an important part of developing health education interventions that effectively promote college students' physical exercise participation and improve their physical health.

Peer support belongs to the category of social support. Mead et al. defined peer support as a system of giving and receiving help based on the key principles of respect, shared responsibility, and mutual help (7). Wentzel et al. defined peer support as the mutual or one-way provision of material help and/or emotional care and companionship, among other behaviors (8). A number of studies have found a positive relationship between peer support and individual physical exercise behaviors. For example, Fitzgerald et al. found that the perceived level of peer support played an important role in adolescent physical exercise behavior among adolescents aged 10–18 years (9). Chen et al. found that peer support enhanced self-efficacy and thus promoted physical exercise frequency among students in grades 9–12 (10). Reimers et al. found that peer support levels were associated with frequency of multiple physical exercise behaviors (outdoor play, sports, or walking transportation) among children aged 6–17 years (11). Sylvia-Bobiak et al. found gender differences in the relationship between peer support and physical exercise behaviors among college students. Peer support influenced physical exercise participation more significantly in male college students than in female college students (12). Therefore, understanding an individual's perceived level of peer support may be helpful in promoting individual physical exercise behaviors.

Existing research has developed a number of measurement instruments to identify individuals' perceived peer support. For example, Zimet et al. designed a measure of peer support in their development of the Multidimensional Scale of Perceived Social Support (MSPSS) (13). Mostafaei et al. designed a peer support scale containing five dimensions: informational support, emotional support, instrumental support, feedback, and companionship support (14). Some social support scales are also often used to measure peer support, such as the child and adolescent social support scale (CASSS) (15), the College Student Social Support Scale (16), and the Social Support Rating Scale (17). However, given the complexity of an individual's perceived peer support, conducting accurate and trustworthy assessments can be a challenge. This is because individuals differ in their behaviors such as providing material help and/or emotional care and companionship to each other or singularly in specific contexts or specific behaviors (9). For example, peer support in a health care context often includes emotional, informational, and assessment support. In this setting, emotional support includes expressions of caring, encouragement, careful listening, reflection, reassurance, and often avoids critical or persuasive advice (18). Informational support is the provision of knowledge related to problem solving, including the availability of relevant resources, independent assessment of the problem, alternative courses of action, and guidance on effectiveness (19). Evaluative support, also known as affirmative support, involves the exchange of information related to self-evaluation and includes affirmation of expressions of emotional, cognitive, and behavioral appropriateness (20). Peer support in the workplace, on the other hand, is more concerned with drawing on life experiences, engaging in mutually beneficial discussions, and so on (21). Therefore, it seems essential to conduct context-specific or behavior-specific peer support assessments. To the best of our knowledge of published articles, there are several assessment tools available to identify social support in physical exercise settings. For example, Zhong et al. developed the Exercise Social Support Scale (22), which contains four dimensions, namely emotional support, informational support, instrumental support, and peer support. Sallis et al. developed the Social Support for Exercise Scale, which contains two dimensions: the Family Support for Exercise Scale and the Friend Support for Exercise Scale (23). Farias et al. developed the Social Support for Adolescent physical exercise Scale (ASAFA), which consists of two dimensions: parental support and friend support (24). However, most of the existing assessment tools consider peer support as a dimension of social support and do not provide a more detailed assessment of the emotional, informational, and behavioral support provided by peers.

Given the current physical health status of Chinese college students, there is a need to develop an assessment tool that can effectively identify the perceived level of peer support among college students in a physical exercise setting. Therefore, this study aimed to design a preliminary peer support questionnaire for physical exercise among Chinese college students and to collect validity evidence for the questionnaire based on the Kane framework (25). The validity evidence included four inferential processes of scoring, generalization, inference, and influence,

thereby objectifying the subjectivity and qualitative nature of college students' perceived levels of peer support in physical exercise settings.

This study follows the Kane framework to produce a workflow that illustrates how it can be used to conduct a validity validation study of the PEPSQ. In a later section of the article, this study describes the study's evaluation setting and evaluation strategy, defines the study's key variables, specifies the study's hypotheses and the evidence collected to test those hypotheses. The results of the evaluation process are also compared to the initial arguments. This study also reflects on and discusses the gaps in the discussion of this study's application of the framework. Using this study's evaluation process, this study demonstrates how to collect empirical data and report the judgment process for PEPSQ validity.

Research method

In collecting and evaluating the validity evidence for the PEPSQ, this study applied the Kane validity framework. In accordance with the characteristics of the Kane framework, decisions must be made prior to the study as to which inferences need to be considered and judgments must be made as to whether the evidence obtained is favorable or unfavorable in the absence of clear guidelines. This research team tested, documented, and reflected on the challenges and final decisions in applying the theory to practice. The following is a specific description of the methodology of this study.

Research overview

Figure 1 illustrates the interpretation of the validity process for this study using the Kane framework.This study focused on the level of perceived peer support among university students in a physical exercise environment. A questionnaire containing five measurement dimensions was initially designed for this study to determine the measurement structure of peer support. The questionnaire addressed interest support, material support, emotional support, behavioral support and information support from peers as perceived by university students in the physical exercise environment. The plan of this study was for the assessor to identify the level of peer support of college students in the physical exercise environment through the PEPSQ and to predict college students' physical exercise behavior based on the results of the PEPSQ scores. Based on this interpretation and use, this study illuminates much of the evidence of validity in the process of constructing the PEPSQ. Based on the Kane framework, this study organizes four validity arguments: scoring, generalization, extrapolation and implication.

In essence, this study traced the assessment of perceived peer support in physical exercise settings among college students. From scoring a single observed entry (scoring), to using observed scores to generate an overall test score representing performance in the testing environment (generalization), to making inferences about what the test score might imply about real-life performance (extrapolation), and then prejudging and making decisions about this information (implication). This study presents this process of validity argumentation using Table 1. Scoring examines the relationship between observed performance and the score or rating generated by that performance; generalization examines the link between a sample of observed performance and the broader domain of all possible performance in the assessment setting; extrapolation focuses on the link between assessment results and other measures of similar performance domains; and implication making examines the integrity of the process leading to the decision and the individual, project or societal Consequences (26).

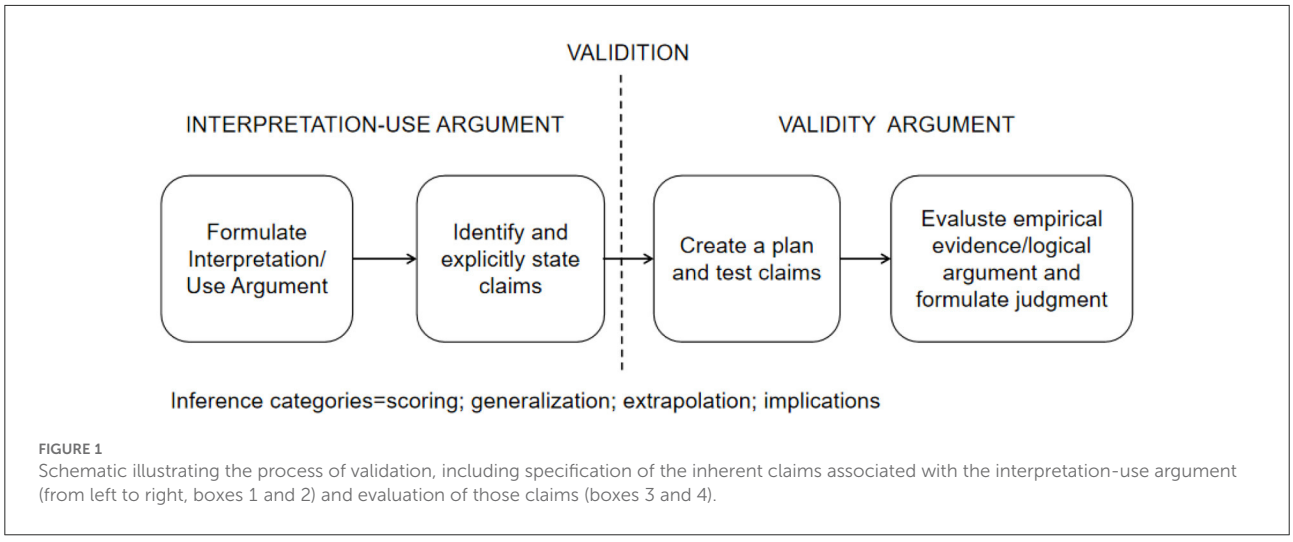

FIGURE 1
Schematic illustrating the process of validation, including specification of the inherent claims associated with the interpretation-use argument (from left to right, boxes 1 and 2) and evaluation of those claims (boxes 3 and 4).

TABLE 1 Specific evidence to support validity arguments.

	Scoring	Generalization	Extrapolation	Implication
Definition of Kane (26)	Rule is appropriate Rule is applied as specified Scoring is free of bias Data fit the scaling todel	Sample is representative of universe of possible observations Sample is large enough to control for random error	Observed score is related to the target score No systematic errors likely to undermine the extrapolation	Implications (interpretations) are appropriate Properties of scores support the implications (interpretations) associated with the label
Operational sources of evidence	Development of scoring dimensions/development of selection items Evidence of independence of scoring dimensions Distinguishability of scored items Evidence of scoring reliability Quality control of scoring	Internal consistency reliability across projects Assessment of sources of measurement error Sampling of observations (number of items or sites, breadth of content) Sample size	Relationships with other variables/measures (correlation with other scores) Development of items to reflect the full breadth of real-life tasks Retesting performance	Impact on the physically exercise person (i.e., viewing the act of assessment as an intervention) Impact on the project Accurate classification of individuals Standard setting process

Analysis plan

This study organized the data collection and analysis of the study by inference categories, scoring, generalization, extrapolation, and implications in the following steps.

In this study, peer support for physical exercise was defined as the behavior of peers providing material help and/or emotional care and companionship in the physical exercise environment and/or physical behavior, either mutually or unidirectionally. Firstly, the core elements of each dimension of the existing questionnaire were analyzed by the subject members based on the literature, for example, the interest support dimension includes interest in the direction of exercise purpose, project hobbies, etc. Secondly, the relevant questions were developed according to the core elements. The sources of questions mainly include the following ways: (1) borrowing and adapting relevant items from established peer support measurement tools at home and abroad, such as the Friendship Quality Scale for Youth Sports in China (SFQA-C) (22), the Questionnaire on Social Support, Motivation and Participation in Sports for Youth (27), and the Questionnaire on the Status of Peer Support and physical exercise for Children and Youth (28), etc. (2) Based on the research and review in the field of factors influencing physical exercise among college students, representative contents were extracted and compiled into test items. (3) Relevant test items were compiled based on the additional contents and expressions of front-line physical education and health course teachers and college students in the open-ended questionnaire. Finally, the topics that best fit the operationalized definition of each dimension and have less crossover between dimensions were selected after discussion by the group, and experts in the field of physical and health education were invited to evaluate the content validity and make suggestions for modification. Finally, the initial questionnaire containing five dimensions and 42 questions was developed.

The first test had a total of three assessors. The second test had a total of six assessors. The assessors were current graduate students. All assessors received training on the item description 1 week prior to the assessment. The training included the conceptual framework of the assessment design, the role of the assessors, and a detailed description of the scoring instrument and how to apply it.

The assessor is primarily responsible for administering the questionnaire. The completion of the assessment questionnaire was done by the subjects themselves. Raters were asked to avoid sharing perceptions of any performance or sharing assigned scores in order to avoid calibration of the rater over time. All data were completed and data collected directly through the electronic questionnaire platform. Each question was scored from 1 (not at all) to 5 (fully). Data analysis calculates the subject's score for individual questions, as well as the score for each dimension and the total score.

The study used the Mack electronic questionnaire platform for data collection. The first survey came from college students in multiple universities in the author's city (352 valid questionnaires). This sample was used to conduct a preliminary exploration of the dimensions of the test questionnaire. The second test came from college students in six Chinese provinces and cities (1,219 valid questionnaires). This sample was used to examine the stability of the questionnaire dimensions and the similarity of students' test scores. The basic information of the respondents of the two surveys is shown in Table 2.

This study hoped to identify the perceived level of peer support among college students in physical exercise settings.

TABLE 2 Personal information of survey respondents.

Test	Gender	*N*	Age (M ± SD)	Household registration type	
				Citie and town	Rural
First test	Male	178	20.12 ± 1.40	16.9%	83.1%
	Female	174	19.94 ± 1.12	20.1%	79.9%
	Total	352	20.03 ± 1.27	18.5%	81.5%
Second test	Male	517	20.15 ± 1.34	16.8%	83.2%
	Female	702	20.02 ± 1.34	20.9%	79.1%
	Total	1,219	20.09 ± 1.34	18.8%	81.2%

Therefore, this study sought additional measures to help validate the performance of the PEPSQ in the real world.The Exercise Social Support Scale (22) developed by Zhong et al. was used in a correlation analysis with this questionnaire to test the inferential effects of the results of this questionnaire test.

The purpose of this study is to construct an assessment tool that can effectively identify the level of perceived peer support among college students in physical exercise setting. Therefore, the peer support scores obtained through the PEPSQ should be able to predict the physical exercise behavior of college students in a real environment. At the same time, the measurement results of PEPSQ should have a certain degree of stability. In this study, 48 college students were randomly selected from the second test for retesting, which was used to test the stability of the PEPSQ assessment results.

Reseach results

Kane's validity framework emphasizes a chain of inferences from score generation to decisions about the ratee, a chain that can be conceptualized as the path that must be followed before sufficient evidence can be obtained. Therefore, the present study reports the results of this study guided by this stepwise conceptualization process.

Evidence of scoring

In this study, a questionnaire analysis was conducted using test data from 352 college students to determine the dimensions and items of the PEPSQ. The independence between the observations was first tested. The results of the autocorrelation test showed a Durbin-Watson value of 1.980, which is relatively close to 2, suggesting that the observations are independent of each other. The results of the item multicollinearity test showed that the VIF were <10 and 1/VIF were >0.1, suggesting that there was no multicollinearity problem. Pearson correlation coefficients between the entry scores and the total questionnaire scores were then tested (Table 3). The results of Pearson correlation coefficients showed that the entry scores were significantly correlated with the total questionnaire scores (p-value $<$ 0 01), and all Pearson correlation coefficients were >0.40. Exploratory factor analysis (inclusion criteria were common factor loadings ≧0.4) was then conducted for all items based on theoretical concepts (29) (Table 4). The results of the exploratory factor analysis showed that the eigenvalues of the four common factors were 12.257, 1.896, 1.530, and 1.115, respectively, with a cumulative variance explained of 69.987%. The final assessment questionnaire obtained was 4 dimensions (interest support, material support, emotional support, and behavioral support) with 24 items (Table 5).

This study used data from 1,219 university students for questionnaire analysis to verify the independence of the questionnaire dimensions. The independence between the observations was first tested. The results of the autocorrelation test showed a Durbin-Watson value of 2.069, which exceeds 2, indicating that the observations are independent of each other. The results of the item multicollinearity test showed that VIF <10 and 1/VIF >0.1, indicating that there is no multicollinearity problem.After testing for entry independence, a validation factor analysis of the questionnaire was conducted using Amos 23.0 software. In the initial model (Table 6), although RMSEA = 0.080 and X^2/df = 4.28 for the model, the significance probability value of $p < 0.05$ reached a significant level, indicating that the fitness of the hypothetical model plot to the observed data needs to be improved and the model needs to be further revised. Therefore, referring to Wu's suggestion (30), it is assumed that for the model to achieve a better fit, a better approach to model revision is to release certain assumptions. The initial model assumes that there is no correlation between the error variables and then, according to the AMOS correction indicator prompt, it is possible to find some degree of covariation in the error variables of some observed variables. If they are reset to have a covariate relationship with each other, the fitness of the model can be optimized. Thus, this study corrected the model according to the maximum correction value class, releasing multiple assumptions one at a time. The revised model obtained after multiple releases had X^2/df = 3.41 and RMSEA = 0.074, with a significance

TABLE 3 Pearson correlation coefficient table.

Coding	Pearson correlation coefficient	Coding	Pearson correlation coefficient	Coding	Pearson correlation coefficient
Q1	0.584**	Q15	0.687**	Q29	0.780**
Q2	0.611**	Q16	0.688**	Q30	0.794**
Q3	0.699**	Q17	0.734**	Q31	0.770**
Q4	0.654**	Q18	0.741**	Q32	0.811**
Q5	0.642**	Q19	0.713**	Q33	0.718**
Q6	0.681**	Q20	0.722**	Q34	0.736**
Q7	0.671**	Q21	0.759**	Q35	0.764**
Q8	0.694**	Q22	0.755**	Q36	0.766**
Q9	0.621**	Q23	0.798**	Q37	0.740**
Q10	0.615**	Q24	0.774**	Q38	0.789**
Q11	0.760**	Q25	0.702**	Q39	0.789**
Q12	0.730**	Q26	0.669**	Q40	0.776**
Q13	0.657**	Q27	0.783**	Q41	0.786**
Q14	0.691**	Q28	0.750**	Q42	0.750**

**$P < 0.01$.

TABLE 4 Standardized factor loading tables.

Coding	Factor loading				Common factor variance
	Factor 1	Factor 2	Factor 3	Factor 4	
Q1		0.714			0.610
Q2		0.798			0.729
Q3		0.751			0.760
Q4		0.731			0.685
Q5		0.782			0.749
Q6		0.707			0.694
Q7		0.585			0.648
Q9			0.656		0.612
Q10			0.743		0.668
Q11			0.579		0.676
Q12			0.619		0.658
Q13			0.770		0.733
Q14			0.700		0.672
Q18	0.609				0.610
Q20	0.751				0.702
Q21	0.685				0.689
Q22	0.742				0.739
Q24	0.757				0.759
Q25	0.797				0.732
Q26	0.752				0.661
Q30				0.685	0.751
Q31				0.795	0.835
Q33				0.809	0.790
Q37				0.622	0.632

TABLE 5 Dimensions and items of PEPSQ.

Dimension	Item description
Interest support	
Q1	I have friends who have the same exercise interests as me
Q2	I have friends who share my exercise purpose
Q3	I have friends who like the same sports stars as me
Q4	I have friends with whom I share the same sports views and ideas
Q5	I have friends with whom I get along well in sports
Q6	I have friends who like the same sports brands as me
Q7	I have friends with whom I talk about solving exercise problems
Material support	
Q9	My friend provided me with books for physical exercise
Q10	My friend provided me with some places to exercise
Q11	My friend provided me with some water or drinks for physical exercise
Q12	My friend provided me with some supplementary food for physical exercise
Q13	My friend helped me buy some clothes for physical exercise (e.g., sports clothes, sports shoes, etc.)
Q14	My friend bought me some sports equipment (e.g., basketball, badminton racket/ball, etc.)
Emotional support	
Q18	When I want to quit sticking to my exercise program, my friends encourage me to keep going
Q20	My friend will comfort me when I have difficulties in physical exercise
Q21	My friend will work with me to solve problems I encounter in physical exercise
Q22	My friend understands how I feel in physical exercise
Q24	My friend encourages me when I am unable to accomplish my exercise goals
Q25	My friends encourage me when I feel inferior because of my poor athletic skills
Q26	My friends take care of me when I get injured in sports
Behavioral support	
Q30	When I don't want to play sports, my friend invites me to play sports
Q31	Even if my friends don't play sports, they will be there for me when I play sports
Q33	Even if my friends have other things to do, they often make time to exercise with me
Q37	My friends will watch some sports programs with me

probability value of $p > 0.05$, which did not reach a significant level, indicating a better fit of the hypothesis model plot to the observed data (see Figure 2). Factor loadings for all entries were above 0.7, indicating good convergent validity for each factor. The revised RMSEA was within an acceptable fit range, although it did not reach the best value recommended by Hu and Bentler (31).

TABLE 6 The results of the questionnaire's structural validity test.

Model	X^2/df	TLI	CFI	RMSEA
Initial model	4.28	0.891	0.901	0.080
Revised model	3.41	0.905	0.917	0.074

Reliability analysis of the questionnaire

In this study, the reliability of PEPSQ was tested by homogeneity test (Cronbach's alpha coefficient) and split-half coefficient (Spearmen-Brown correlation coefficient). The specific test results are shown in Table 7. The results of the homogeneity test and the split-half coefficient test indicate that the reliability of the PEPSQ is good. Meanwhile, the results of the correlation analysis between the total score of each dimension of PEPSQ and the total score of the questionnaire showed that the correlation coefficients of interest support, material support, emotional support, and behavioral support and the total score of the questionnaire were 0.773, 0.868, 0.884, and 0.914, respectively, indicating that PEPSQ has good reliability (32).

Evidence of generalization

The overall Cronbach's α coefficient of the PEPSQ was 0.902, indicating that the PEPSQ has good internal consistency. Table 8 shows the results of the analysis of entry reliability, and the Cronbach's α coefficient and corrected total correlation (CITC value) after removing an entry are provided in the table, respectively.

This study was conducted in both test samples and the sampling strategy was tested for adequacy in establishing a reliable hypothesis for identifying the level of perceived peer support among college students in physical exercise setting. Using data from a sample of 1,219 college students, the study ranked the PEPSQ scores from highest to lowest. The respondents in the top and bottom 25% of the total PEPSQ scores were named as high and low subgroups, and independent sample *t*-tests were conducted for each entry. The results of the analysis are presented in Table 9. The results indicate that the t-statistic (i.e., the decision value) for each entry was >10 and that the scores were significant between the high and low subgroups (p-value < 0.01). The findings suggest that the sampling strategy of this study is sufficient to establish a reliable identification

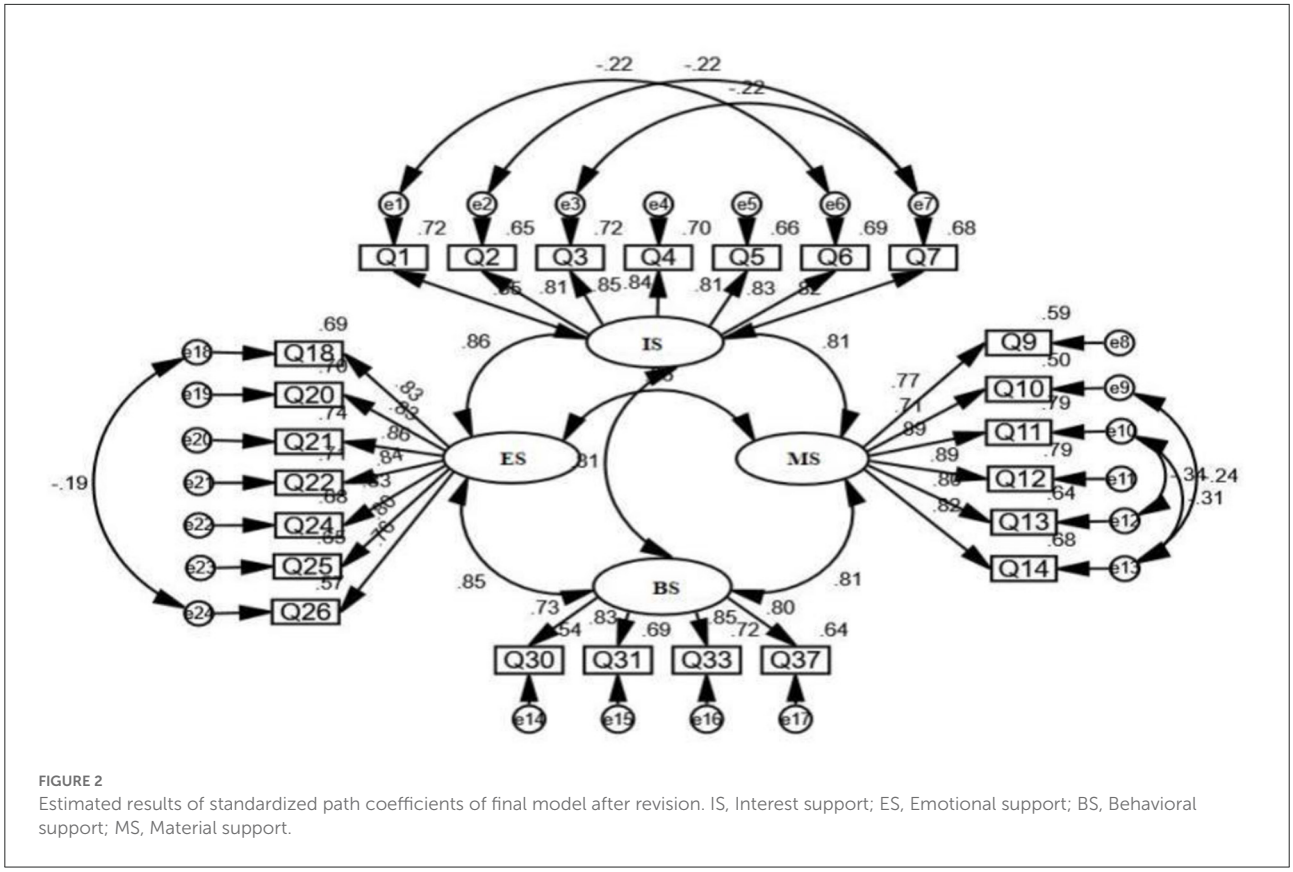

FIGURE 2
Estimated results of standardized path coefficients of final model after revision. IS, Interest support; ES, Emotional support; BS, Behavioral support; MS, Material support.

TABLE 7 Questionnaire dimensions and reliability coefficients.

Dimension	Number of items	Cronbach's α	Spearman-brown correlation coefficient
Interest support	7	0.900	0.851
Material support	6	0.890	0.856
Emotional support	7	0.913	0.876
Behavioral support	4	0.844	0.846
PEPSQ	24	0.902	0.899

of college students' perceived level of peer support in physical exercise settings.

Evidence of extrapolation

The Exercise Social Support Scale was used as the validity standard of PEPSQ. The correlation test results showed that the correlation coefficients of the PEPSQ dimension scores and total scores with the exercise social support scale dimension scores and total scores reached a significant level of $P < 0.01$. This indicates that the PEPSQ has good validity of the validity scale correlation validity to identify the perceived peer support of college students in the physical exercise environment. The results of the analysis are shown in Table 10.

This study further examined the retest reliability of the PEPSQ at 2-week intervals. The results showed that the data of both tests reached a significance level of $p < 0.01$ for all dimensions, and the retest reliability was above 0.7 for all dimensions, indicating that the PEPSQ measures have some stability.

Evidence of implications

The results of this study suggest that researchers or educators can use the PESCQ to differentiate between groups of college students who participate in physical exercise or who do not, and target interventions to different groups, which has implications for practical application. The results of the analysis are shown in Table 11.

Discussion

With reference to Kane's validity framework, this study presents the research process and results of this study by

TABLE 8 Results of the reliability analysis of the items.

Coding	CITC	The alpha coefficient of the deleted term	Cronbach alpha coefficient
Q1	0.625	0.901	0.902
Q2	0.492	0.901	
Q3	0.520	0.901	
Q4	0.539	0.901	
Q5	0.495	0.901	
Q6	0.626	0.901	
Q7	0.617	0.901	
Q9	0.640	0.900	
Q10	0.571	0.901	
Q11	0.766	0.894	
Q12	0.674	0.900	
Q13	0.703	0.900	
Q14	0.692	0.900	
Q18	0.830	0.892	
Q20	0.724	0.900	
Q21	0.665	0.901	
Q22	0.697	0.901	
Q24	0.678	0.901	
Q25	0.660	0.901	
Q26	0.711	0.900	
Q30	0.727	0.900	
Q31	0.751	0.900	
Q33	0.784	0.900	
Q37	0.680	0.901	

TABLE 9 Results of the discrimination analysis of items.

Coding	Mean ± SD		*T*-value	*P*-value
	High grouping ($N = 318$)	Low grouping ($N = 304$)		
Q1	3.98 ± 0.86	2.56 ± 0.93	10.593	<0.01
Q2	4.09 ± 0.71	2.76 ± 1.01	10.196	<0.01
Q3	4.14 ± 0.64	2.47 ± 0.90	14.383	<0.01
Q4	4.07 ± 0.77	2.60 ± 0.95	11.310	<0.01
Q5	4.18 ± 0.66	2.86 ± 0.94	10.884	<0.01
Q6	4.23 ± 0.66	2.72 ± 0.96	12.251	<0.01
Q7	4.09 ± 0.71	2.58 ± 1.01	11.529	<0.01
Q9	3.89 ± 0.79	2.48 ± 0.96	10.769	<0.01
Q10	3.86 ± 0.91	2.23 ± 0.88	12.223	<0.01
Q11	4.20 ± 0.68	2.22 ± 0.90	16.536	<0.01
Q12	4.00 ± 0.73	2.26 ± 0.86	14.579	<0.01
Q13	3.73 ± 0.89	2.06 ± 0.85	12.875	<0.01
Q14	4.02 ± 0.68	2.27 ± 0.91	14.603	<0.01
Q18	4.10 ± 0.61	2.40 ± 0.99	13.795	<0.01
Q20	4.12 ± 0.66	2.57 ± 0.91	13.069	<0.01
Q21	4.16 ± 0.58	2.52 ± 0.90	14.506	<0.01
Q22	4.26 ± 0.55	2.66 ± 0.90	14.369	<0.01
Q24	4.27 ± 0.59	2.60 ± 0.86	15.024	<0.01
Q25	4.21 ± 0.64	2.75 ± 0.87	12.719	<0.01
Q26	4.27 ± 0.56	2.83 ± 1.03	11.605	<0.01
Q30	4.16 ± 0.73	2.32 ± 0.89	15.152	<0.01
Q31	4.04 ± 0.77	2.15 ± 0.95	14.644	<0.01
Q33	3.92 ± 0.82	2.18 ± 0.92	13.453	<0.01
Q37	4.14 ± 0.72	2.30 ± 0.94	14.778	<0.01

inference category. As noted above, this drove the data collection and analysis plan for this study. This study operationalised the corresponding validity evidence that the study needed to demonstrate in response to Kane's conceptual definition of scoring, generalization, extrapolation, and implications. This evidence can help to develop support for the validity of the PEPSQ, as well as inferences based on the scores generated.Kane's validity framework emphasizes a chain of inferences from score generation to inference about the test taker's decision, a chain that can be operationalised as a path that must be followed before sufficient evidence can be obtained. Therefore, the operationalisation of this step is used as a guide to report the results of this study.

To form validity arguments, Kane suggested evaluating the evidence and deciding whether to accept or reject it, and/or modify the process and/or the proposed use. In the scoring evidence, evidence of PEPSQ dimensional independence, and evidence of entry differentiation were validated. In the Generalization evidence, both sampling data showed that the sampling strategy of this study was sufficient to establish a reliable identification of college students' perceived level of peer support in physical exercise settings. In the Extrapolation evidence, the results of the correlation analysis using the Exercise Social Support Scale with this questionnaire showed that the assessment process of this study would predict future real-world performance in real-world physical exercise settings. Also the small-sample retest reliability in meeting the hypothesis (medium to high level) indicates that the PEPSQ measures have some stability.In Implications evidence, given our homogeneity and highly selected participants, the study tested the assessment results to predict physical exercise behavior in real exercise settings. The results of the study showed that the regular exercise group had significantly higher scores and total scores in interest support, material support, emotional support and behavioral support than the university students in the no regular exercise group. It is suggested that the assessment results of this study can predict the real behaviors in physical exercise settings.

Although the four inferred results of this study are relatively positive to illustrate the validity of the PEPSQ. However, this series of processes is primarily intended to illustrate that this

TABLE 10 Correlation analysis results.

	Interest support	Material support	Emotional support	Behavioral support	PEPSQ
Instrumental support	0.453**	0.630**	0.514**	0.678**	0.659**
Informational support	0.479**	0.547**	0.490**	0.543**	0.603**
Affective support	0.468**	0.457**	0.648**	0.464**	0.608**
Peer support	0.419**	0.622**	0.554**	0.627**	0.647**
ESSS	0.517**	0.651**	0.624**	0.669**	0.720**

**$P < 0.01$.

TABLE 11 Comparison of PEPSQ scores of different groups.

	Regular exercise group ($n = 155$)	No regular exercise group ($n = 1,064$)	T-value
–	24.38 ± 5.18	21.31 ± 5.05	4.727**
Material support	19.22 ± 4.68	16.61 ± 4.49	4.448**
Emotional support	24.56 ± 5.18	21.90 ± 5.39	4.044**
Behavioral support	12.89 ± 3.41	11.22 ± 3.44	3.807**
PEPSQ total score	81.05 ± 15.81	71.04 ± 15.42	5.035**

**$P < 0.01$.

study's argument for PEPSQ validity is not a conclusion, but rather represents a series of positive steps in research aimed at building and refining the evidence for PEPSQ validity.

Applying Kane's validity framework, this study's argument for the validity of the PEPSQ is demonstrated through an operationalised argument for four processes: scoring, generalization, extrapolation, and implications. Reflecting on the entire process of this study, the Kane framework helped structure the study's organizational and analytical framework. The validity of the PEPSQ is a chain of evidence strung together. However, in this study, challenges were encountered in deciding how to prioritize the collection and reporting of evidence across the four inferential dimensions. Because there is a paucity of research literature related to physical exercise peer support, this made it difficult for the research team to determine from the available studies which weak and problematic links must be prioritized in the design of this study. Therefore, the research design for the weak and problematic links in this study may not be adequate and may leave important evidence gaps in the validity argument.

At the same time, there are some limitations in this study. First, the stability of the study results may be affected by the sample data in this study due to the sampling method, and further validation through a large national sample data is needed in the future. Second, these data were obtained from the subjects' self-assessment reports, and the data results may be affected by the subjects' text reading comprehension ability, and their understanding of the questionnaire items may vary. Finally, the evidence for the four inferential processes in this study was based only on subjects who completed the questionnaire in its entirety, which resulted in a lower error rate for the questionnaire, but this may have partially influenced the results of the test.

Conclusion

The PEPSQ, developed in this study, has four dimensions and twenty-four items. This study used the Kane validity framework to identify and examine the validity process of the PEPSQ. Evidence based on the four inferential processes of scoring, induction, extrapolation, and influence of the Kane framework supports that the PEPSQ can be used to measure the level of perceived peer support in physical exercise settings among Chinese college students.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review and Approval of the Academic Committee of the Physical Education College of Guizhou Normal University (No. 20210310). The patients/participants provided their written informed consent to participate in this study.

Author contributions

XY, LL, and NS conceived the study and performed data analysis and interpretation. LL and XY prepared the manuscript. LZho, LZha, YY, and JY participated in data collection. XZ was involved in the revision of the paper. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.871306/full#supplementary-material

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