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Effect of BMI on Mortality in Patients With Tuberculosis and HIV Coinfection in Asia and Africa: Systematic Review and Meta-Analysis

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Abstract

Background: Tuberculosis (TB) continues to pose a major global health threat, particularly in low- and middle-income countries. An estimated 10.8 million people developed TB in 2023, corresponding to 134 cases per 100,000 population. The Southeast Asia region accounted for 45% of global TB incidence, while the African region contributed 24%. Nutritional status, particularly low BMI, is a key modifiable determinant of adverse clinical outcomes. However, its overall impact on mortality among TB-HIV coinfecting populations in Asia and Africa remains poorly quantified.

Objective: This study aimed to systematically assess the association between BMI and mortality among patients with TB-HIV coinfection in Asia and Africa.

Methods: A systematic review and meta-analysis were conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. Cohort studies published between 2000 and 2024 were identified through PubMed, Scopus, and ProQuest. Data extraction and risk of bias assessment were performed independently by 3 reviewers using the Risk of Bias in Non-Randomized Studies – of Exposure tool. A random effects model with the DerSimonian-Laird method was applied using RevMan 7.2 (Cochrane) to estimate pooled risk ratios with 95% CI. Heterogeneity was quantified using the I^2 statistic, and subgroup analyses were conducted by geographic region.

Results: Seven cohort studies met the inclusion criteria. The pooled estimate indicated that patients with BMI less than 18.5 kg/m² had approximately twofold higher mortality risk compared to those with normal or higher BMI (risk ratio=2.01; 95% CI 1.63 - 2.48; $P<.001$). Despite moderate heterogeneity ($I^2=64%$), the association remained consistent across subgroups. Although most studies were rated as having high or moderate risk of bias, sensitivity analyses confirmed the robustness of the results.

Conclusions: Low BMI significantly increases the risk of mortality among patients with TB and HIV coinfection in Asia and Africa, underscoring its prognostic and modifiable role in clinical outcomes. Routine nutritional screening, BMI monitoring, and targeted supplementation should be integrated into national TB-HIV management programs, particularly in resource-limited settings. Strengthening TB-HIV nutrition service integration is essential to improve survival and achieve global End TB and United Nations Programme on HIV/AIDS 95-95 - 95 targets.

Trial Registration: OSF Registries osf.io/74qwh/; <https://osf.io/74qwh/overview>

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KEYWORDS

Asia; Africa; BMI; HIV; meta-analysis; mortality; tuberculosis

Introduction

Tuberculosis (TB) and HIV represent 2 converging epidemics that amplify each other's clinical and epidemiological impact. This syndemic interaction remains one of the most formidable challenges to achieving global health targets. TB and HIV

remain major global public health threats, particularly in low- and middle-income countries [1]. The interaction between TB and HIV is synergistically detrimental, as HIV significantly increases the risk of progression from latent TB infection to active disease, while TB accelerates the progression of HIV-related immunosuppression [2,3]. In 2023, an estimated

10.8 million people developed TB globally, an increase from 10.7 million in 2022, reflecting a continued rebound following disruption caused by the COVID-19 pandemic. TB caused an estimated 1.25 million deaths, including 161,000 deaths among people living with HIV. Although mortality has declined by 23% since 2015, this progress remains far below the End TB Strategy milestone of a 75% reduction by 2025 [4]. These figures underscore the urgent need for integrated approaches to meet the World Health Organization End TB Strategy and United Nations Programme on HIV/AIDS 95-95 - 95 targets, which emphasize early detection, treatment adherence, and reduction of preventable deaths.

The burden of TB is disproportionately concentrated in low- and middle-income countries, particularly in Asia and Africa, which together account for nearly 87% of global incident cases. A total of 5 countries—India, Indonesia, China, the Philippines, and Pakistan—alone contribute more than half of the global TB burden. The African region continues to experience the highest mortality rate, estimated at 24 deaths per 100,000 population among HIV-negative individuals, compared with only 2.4 in the European region. Coinfection with HIV remains a major driver of mortality, with an estimated 662,000 people living with HIV developing TB in 2023, yet only 58% receiving both TB treatment and antiretroviral therapy (ART) [4].

Several factors exacerbate TB-HIV transmission and mortality. These include socioenvironmental determinants such as poverty, overcrowding, malnutrition, smoking, and exposure to environmental pollutants like biomass fuel and mining dust [5-7]. HIV infection independently contributes to poor nutritional status, which in turn influences TB disease progression and treatment outcomes [8-10]. Compounding this, the COVID-19 pandemic disrupted TB diagnostic and treatment services globally, particularly in Africa and Asia-Pacific, leading to delayed case detection and treatment initiation [11].

Among the modifiable determinants of survival, nutritional status, particularly BMI, plays a crucial role. From a biological standpoint, low BMI reflects impaired nutritional and immunological status, which weakens host defense mechanisms and predisposes patients to severe disease progression and poor treatment outcomes. Undernutrition remains the leading global risk factor for TB incidence, surpassing HIV, diabetes, and alcohol use in its attributable burden. Low BMI (<18.5 kg/m²) has consistently been linked to increased early and all-cause mortality during TB treatment [12]. A prospective cohort study in Ethiopia demonstrated that BMI improvement following initiation of ART was significantly associated with reduced mortality, regardless of initial BMI classification [13]. In contrast, BMI decline within the first month of TB treatment was linked to higher mortality among HIV-positive individuals in Myanmar and Zimbabwe [14]. Additional evidence from Taiwan suggests that underweight male patients have significantly higher TB-specific and non-TB-specific mortality risks during treatment [15].

HIV-associated wasting, often reflected by reduced midupper arm and muscle circumference, further highlights the intersection between nutrition and immune function in TB-HIV management [8,16]. While early ART initiation alongside TB

therapy—especially for individuals with cluster of differentiation 4 positive (CD4+) counts less than 50 cells/μl—has been shown to improve survival [17], nutritional assessment and interventions remain underintegrated in TB-HIV care programs, particularly in resource-limited settings.

Despite a growing body of research examining the relationship between BMI and mortality in patients with TB and HIV coinfection, the evidence remains fragmented and inconsistent. Existing studies vary widely in design, sample size, and nutritional cut-off definitions, resulting in heterogeneous findings and limiting the reliability of pooled mortality estimates. Furthermore, no comprehensive systematic review or meta-analysis has been conducted to quantitatively synthesize the magnitude of this association, particularly within high-burden settings such as Asia and Africa, where the dual epidemics of TB and HIV intersect with widespread malnutrition. This lack of consolidated evidence has hindered the development of integrated clinical-nutritional strategies aimed at improving survival among patients with coinfection.

Therefore, this study aims to fill this critical gap by conducting a systematic review and meta-analysis of cohort studies evaluating the effect of BMI on mortality among patients with TB-HIV coinfection in Asia and Africa. This study provides the first quantitative synthesis focusing specifically on Asia and Africa—regions that jointly bear nearly 90% of the global TB burden—offering critical evidence to guide regionally tailored public health interventions. We hypothesize that a lower BMI (<18.5 kg/m²) significantly increases the risk of mortality compared to a normal or higher BMI (≥18.5 kg/m²). The results of this study are expected to provide robust, evidence-based insights to guide targeted clinical interventions and public health strategies for this highly vulnerable population.

Methods

Ethical Considerations

This study was conducted using secondary data. This systematic review and meta-analysis is being reported in accordance with the reporting guidance provided in the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol) statement [18-20] (Checklist 1).

Eligibility Criteria

Eligibility criteria for this review included cohort studies (retrospective or prospective) published in the period 2000 - 2024 in PubMed, Scopus, and ProQuest databases, with a focus on adult patients (>15 y) with TB and HIV coinfection in Asia and Africa. Only academic journal articles with full-text access were included, while literature reviews, case reports, short reports, proceedings, and studies without mortality data were excluded. The primary outcome evaluated was mortality in populations with TB or HIV coinfection, so studies that did not report mortality rates or examine pediatric populations were excluded from the analysis.

Data Sources and Search Strategy

A comprehensive literature search was conducted in PubMed, Scopus, and ProQuest to identify relevant studies from

2000 - 2024. The search strategy combined Medical Subject Heading (MeSH) terms and free-text keywords related to TB-HIV coinfection, BMI, and mortality. Only studies published in English and involving adult populations (>15 y) were included. Mendeley reference management software (Elsevier) was used to import and maintain the retrieved studies. On October 30 - 31, 2024, a search was done to find studies that would be suitable for meta-analysis and systematic review. The full boolean search string used was (“Coinfection”[Mesh] OR “Co-infection” OR “Multiple infection”) AND (“Tuberculosis”[Mesh] OR “TB” OR “Tuberculosis”) AND (“HIV Infections”[Mesh] OR “HIV” OR “Human Immunodeficiency Virus” OR “TB?HIV”) AND (“Adult”[Mesh] OR “Mature” OR “Person over 18”) AND (“Body Mass Index”[Mesh] OR “BMI”) AND (“Mortality”[Mesh] OR “Fatal*” OR “Death” OR “Case fatality rate” OR “Mortality rate”) AND (“Cohort Studies”[Mesh] OR “Cohort study” OR “Cohort”).

Screening and Selection Process

A total of 3 independent reviewers participated in the methodical and comprehensive screening and research selection procedure. To make it easier to filter titles and abstracts based on preset inclusion and exclusion criteria, all database search results were uploaded to the Rayyan artificial intelligence app (Rayyan Systems, Inc). Before moving on to the full-text screening phase, which was also carried out individually by the 3 reviewers, articles that were found to be duplicates were eliminated. Discussion and agreement were used to settle any disagreements. Data such as author name, year of publication, area, sample size, and number of events in the experimental group (BMI <18.5 kg/m²) and the control group (BMI ≥18.5 kg/m²) were retrieved from publications that satisfied the selection criteria. The data were then recorded in Microsoft Excel spreadsheets to facilitate further management and analysis.

Risk of Bias Assessment

The risk of bias assessment in this study was performed using the Risk of Bias in Non-Randomized Studies – of Exposure (ROBINS-E) tool, which was specifically developed for evaluating nonrandomized observational studies that investigate the relationship between exposures and outcomes [21]. This tool is particularly appropriate for the present meta-analysis, as all included studies examined the effect of BMI as an exposure on mortality outcomes among patients with TB and HIV coinfection. ROBINS-E assesses 7 domains of potential bias: (D1) bias due to confounding, (D2) bias arising from measurement of the exposure, (D3) bias in selection of participants into the study, (D4) bias due to postexposure interventions, (D5) bias due to missing data, (D6) bias arising from measurement of the outcome, and (D7) bias in selection of the reported result.

Each domain was rated as “low risk,” “some concerns,” or “high risk,” and the overall risk of bias for each study was determined based on the highest level of bias observed across all domains. The use of ROBINS-E was supported by its ability to provide a structured and transparent framework for assessing the internal validity of exposure-outcome relationships in epidemiologic research [22].

Data Extraction

A total of 3 independent reviewers performed data extraction using a standardized Microsoft Excel spreadsheet developed based on a predefined checklist. Extracted information from each primary study included the author’s name, year of publication, study location, sample size, study design, and the number of deaths and survivors in both groups: the experimental group (BMI <18.5 kg/m²) and the control group (BMI ≥18.5 kg/m²). Any discrepancies between reviewers were resolved through discussion and consensus to ensure data accuracy and consistency prior to quantitative synthesis.

Outcome Variable and Measures

The primary outcome assessed in this review was mortality among patients with TB and HIV coinfection, measured as the proportion of deaths between the experimental group (BMI <18.5 kg/m²) and the control group (BMI ≥18.5 kg/m²). The measure of association used was the risk ratio (RR) with a 95% CI. For studies that reported odds ratios or hazard ratios, the estimates were converted into RR values using the method proposed by Zhang and Yu (1998) [23], which adjusts for baseline risk in the control group. This standardization ensured that all effect measures were expressed on a comparable scale, facilitating accurate pooling in the meta-analysis.

Data Synthesis and Analysis

The quantitative synthesis was conducted using Review Manager (RevMan) version 7.2 (Cochrane), applying a random effects model (DerSimonian-Laird method) to account for potential heterogeneity between studies [24]. The pooled effect estimates were expressed as RR with corresponding 95% CI. Heterogeneity was quantified using the *I*² statistic, categorized as low (<25%), moderate (25% - 50%), or high (>50%) [25]. Subgroup analyses were performed based on geographical region (Africa and Asia) to explore potential sources of heterogeneity and assess regional differences in the effect of BMI on mortality. The overall and subgroup pooled estimates were visualized using forest plots.

Protocol Registration and Deviations

This systematic review and meta-analysis was prospectively registered in the Open Science Framework (OSF.IO/74QWH). Minor deviations occurred between the registered protocol and the final analysis. Specifically, the risk of bias tool was changed from the Hoy tool to the ROBINS-E instrument to better align with cohort study designs. These modifications were made prior to data synthesis and did not affect the overall analytic framework or study objectives.

Results

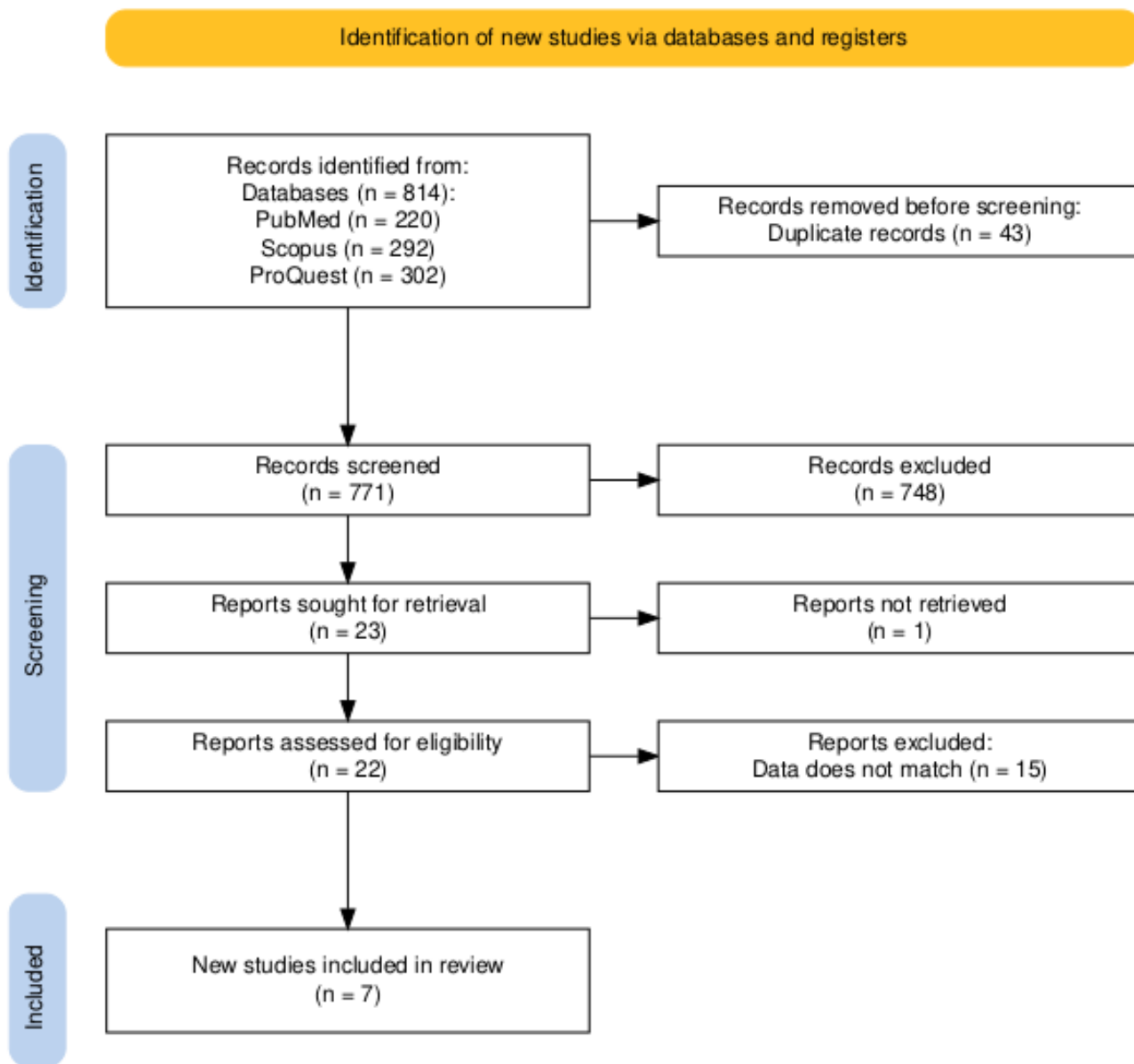
Selection of Studies

A comprehensive literature search yielded 814 articles from 3 major databases, namely PubMed (n=220), Scopus (n=292), and ProQuest (n=302). After 43 duplicate articles were removed, a total of 771 articles were screened at the title and abstract screening stage, of which 748 were excluded as they did not meet the inclusion criteria. A total of 23 articles were then retrieved for full review, but 1 article could not be retrieved, so

22 articles were assessed for eligibility. At this juncture, 15 studies that failed to meet the requisite data criteria were excluded, resulting in the inclusion of 7 articles in the systematic review and meta-analysis [14,26-32]. The study selection

process is detailed in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Findings

The characteristics of the included studies are summarized by key baseline demographic, clinical, and epidemiological features of TB-HIV coinfecting populations across the seven cohort studies. These features include variations in age distribution,

sex composition, nutritional status as measured by BMI, HIV clinical stage, CD4 cell count categories, and ART status at baseline. These variables provide essential context for understanding population heterogeneity and for interpreting the pooled mortality estimates derived from the meta-analysis, as detailed in Table 1.

Table . Data extraction from the included studies.

Author(s) [reference]	Key baseline characteristics ^h	Method	Population/sample	Result
Kegne et al [26]	<ul style="list-style-type: none"> • Age distribution: <15 (3.7%), 15-24 (9.5%), 25-34 (36.7%), 35-44 (31.4%), ≥45 (18.7%) • Sex: Male (56.6%), Female (43.4%) • BMI categories: <18.5 (40.1%), 18.5-24.5 (47.6%), >24.5 (12.2%) • WHO^a HIV clinical stage: Stage I (6.0%), II (4.7%), III (44.9%), IV (44.4%) • CD4^b count (cells/μL): <200 (24.2%), ≥200 (75.8%) • ART^c status/adherence: good (88.3%), fair (7.0%), and poor (4.7%) • Variables NR^d: symptomatic TB status, household TB contact, and viral load 	A retrospective cohort study was conducted among patients coinfecting with TB ^e -HIV who were treated for TB at public health facilities in Bahir Dar city	The study included 401 patients coinfecting with TB-HIV treated between July 2018 and June 2022	Among the 401 patients monitored, 59 (14.7%) passed away during the follow-up period. The research identified several significant predictors of mortality related to BMI. Specifically, patients with a BMI of less than 18.5 kg/m ² experienced a mortality risk that was 3 times higher than those with a normal BMI. This finding was substantiated by an aHR ^f of 3.00, with a 95% CI ranging from 1.44 to 6.28, indicating a statistically significant relationship between lower BMI and increased mortality risk (<i>P</i> <.05) [26]
Bayowa et al [27]	<ul style="list-style-type: none"> • Age distribution: mean 34.6 (SD 10.5); categories <35 (51.54%), ≥35 (48.46%) • ART status at baseline: on ART (95.5%); ART-naïve (4.5%) • ART regimen: 1st line (62.1%); 2nd line (4.4%); and 3rd line (33.4%) • Viral load categories: detectable (9.7%); undetectable (14.4%); and unknown (75.9%) • BMI categories: <18.5 (36.67%); ≥18.5 (63.33%) • Variables NR: symptomatic TB status, household TB contact, newly initiated ART, CD4 count, WHO HIV stage 	The study used a retrospective cohort design that involved reviewing medical records of patients coinfecting with DR-TB ^g and HIV who were registered at the Mulago Tuberculosis Unit from January 1, 2014, to December 31, 2019	The study included 390 participants who met the eligibility criteria of having confirmed DR-TB and documented HIV positive status, resulting from an initial review of 412 records. Participants were aged from 1 to 80 y, with a mean age of 34.6 y (SD 10.5), and the majority were male participants (53.9%).	The results indicated a mortality rate of 33.2% (95% CI 28.7-38.1) among the study population. Specifically, regarding the relationship between BMI and mortality, a BMI of less than 18.5 kg/m ² was associated with an increased likelihood of death. The adjusted incidence rate ratio for those with BMI less than 18.5 kg/m ² was 0.91 (95% CI 0.85-0.97), with a <i>P</i> value of .007, which suggests a statistically significant protective effect against mortality for individuals with a higher BMI. This highlights the critical importance of maintaining an adequate nutritional status as a determinant of mortality outcomes in this vulnerable population [27]
Gevorgyan et al [28]				

Author(s) [reference]	Key baseline characteristics ^h	Method	Population/sample	Result
	<ul style="list-style-type: none"> • Age distribution: ≤37 (8.3%); 31-40 (32.8%); 41-50 (32.8%); >50 (26.2%) • ART status at baseline: favorable (74.4% on ART); unfavorable (51.1% on ART) • CD4 count (cells/mm³): ≤50 (27.6%); 51-200 (18.5%); >201 (17.7%); unknown (55.3%) • BMI: underweight (27.4%); normal (45.6%); overweight or obese (8%) • Variables NR: Symptomatic TB status, household TB contact, viral load, WHO HIV stage. 	<p>The study was conducted in Armenia and used a cohort study design using routine programmatic data of HIV-associated patients with TB receiving treatment from 2015 to 2019.</p>	<p>The population for this research included both pulmonary and extrapulmonary patients with HIV-associated TB, and the study comprised a total of 351 treatment episodes involving 320 individual patients. The authors detailed the sociodemographic and clinical characteristics of these patients through data collected from the National TB database, National HIV database, and patients' medical records.</p>	<p>The results indicated a significant association between BMI and mortality rates among the patients with HIV-associated TB. Specifically, underweight patients had an increased risk of death, reflected in an aHR of 2.5 (95% CI 1.3-4.5), with a <i>P</i> value of less than .01. This finding underscores the critical role of nutritional status in influencing health outcomes within this vulnerable population, highlighting the necessity for addressing malnutrition as a part of TB management and care protocols in clinical settings [28]</p>

Kosgei et al [29]

<ul style="list-style-type: none"> • Age distribution: 15-24 (11.7%); 25-29 (20.7%); 30-34 (23.8%); 35-39 (20.2%); 40-44 (15%); 45-49 (8.6%). Mean age in years (SD) was 33.3 (7.5) • BMI: <15 (12.1%); 15-18.5 (40.8%); 18.5-24.9 (34.1%); >25 (3.1%); missing (9.9%) • Time of ART start after TB treatment: <14 days (23.1%); 15-30 days (13.3%); 31-60 days (10.1%); >60 days (7.4%); before TB treatment (29%); not started (17.1%) • Variables not reported (NR): Symptomatic TB status, household TB contact, CD4 count, viral load, WHO HIV stage 	<p>This study used a retrospective cohort design, analyzing healthcare records from individuals treated for TB between 2012 and 2015. The primary outcome of interest was all-cause mortality during TB treatment.</p>	<p>The study analyzed a total sample of 9026 patients with smear-positive pulmonary TB, aged 15-49 y, who were coinfecting with HIV.</p>	<p>The findings revealed that men exhibited a higher mortality rate (11%) compared to women (9%), with a statistically significant difference (<i>P</i>=.004). The risk ratio indicated that women had a 17% reduced risk of mortality compared to their male counterparts (aHR 0.83; 95% CI 0.72-0.96; <i>P</i>= .013). A higher BMI was associated with a reduced risk of death during treatment; specifically, those with a BMI higher than 18.5 had a lower mortality risk compared to those with a BMI less than 15, underscoring the importance of maintaining a healthy body weight in this population for better treatment outcomes. These results suggest that both gender and BMI significantly influence survival among patients coinfecting with pulmonary TB-HIV, highlighting areas for targeted interventions in health care delivery [29]</p>
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Naidoo et al [30]

Author(s) [reference]	Key baseline characteristics ^h	Method	Population/sample	Result
	<ul style="list-style-type: none"> Age distribution: median age by BMI groups: 33-36 y (IQR 29-43) ART baseline status: uniform (all initiated ART); detailed categories not reported CD4 count groups: only continuous medians available Viral load categories: only mean viral load reported WHO HIV stage: stage 1-3 and 4 reported by BMI Variables not reported: symptomatic TB status, household TB contact 	This study used a retrospective cohort design. Clinical data from HIV-infected patients was evaluated, using statistical methods to assess the correlation between BMI and mortality outcomes. Key analysis tools included multivariate proportional hazards regression to adjust for confounding variables and the log-rank test for comparing survival distributions across BMI categories.	The study comprised a total of 1000 HIV-infected patients. However, due to missing height or weight measurements for 52 patients, the final analysis included 948 patients, split into different BMI categories for assessment. Among these, 389 patients were also coinfecting with TB.	The findings indicated that underweight patients (BMI < 18.5 kg/m ²) faced a significantly increased risk of mortality compared to those with a normal BMI (18.5-24.9 kg/m ²). Specifically, the aHR for mortality in underweight patients was 2.9 (95% CI 1.5-5.7; <i>P</i> =.002). This result underscores a notable correlation between low BMI and elevated mortality rates among HIV-infected individuals, highlighting that underweight patients possessed a nearly threefold elevated risk of death relative to their normally weighted counterparts. The study confirms the essential role of baseline BMI as a prognostic indicator, irrespective of TB coinfection status. Notably, mortality rates for those categorized as overweight (BMI 25.0-29.9) and obese (BMI ≥ 30.0) were not significantly different from those with normal BMI, further establishing the critical impact of being underweight on survival outcomes in this population [30]
Wejse et al [31]	<ul style="list-style-type: none"> Age distribution: 15-30 (46%); 30-40 (24%); 40-50 (16%); >50 (14%) All symptomatic; duration reported; asymptomatic NR. HIV status categories: HIV-negative (71.1%); HIV-1 (18.4%); HIV-2 (7.1%); dual (3.4%) CD4 count (cells/mm³): >500 (9.7%); 200-500 (4.9%); <200 (13.3%) Variables NR: Household TB contact, ART baseline status, viral load, WHO HIV stage 	The study used a longitudinal, prospective cohort design. Patients were identified through daily visits by field assistants to local health centers and a national referral TB hospital. The diagnosis of TB was made according to WHO criteria, and both smear-positive and smear-negative cases were included based on defined medical and clinical parameters.	The study included a total of 1312 patients with TB who had completed their anti-TB treatment by September 1, 2013. Among these patients, 379 were HIV-infected, comprised of those with HIV-1, HIV-2, and dual infections.	The findings of the study indicated a significant relationship between BMI and mortality among patients with TB. Specifically, the results demonstrated that patients with a BMI less than 17 kg/m ² had a crude hazard ratio of 1.42 (95% CI 0.81-2.49), and this association reached statistical significance with a <i>P</i> value of .021. This emphasizes that lower BMI is correlated with increased mortality rates in the context of TB management. The study underscores the necessity of monitoring and addressing nutritional status as a critical component of TB treatment protocols [31]
Benova et al [14]				

Author(s) [reference]	Key baseline characteristics ^h	Method	Population/sample	Result
	<ul style="list-style-type: none"> Age distribution: median (34-y-old); IQR (29.5-40.2) BMI: <16 (23.6%); 16-18.49 (36.8%); 18.5-24.99 (36.8%); ≥25 (2.8%) ART status at TB treatment start: prior to TB treatment (21.3%); within 2 wk (8.7%); within 2-4 wk (18%); after 4 wk (31.9%); after end of TB treatment (20.1%) CD4 count (cells/mm³): ≤100 (57.8%); 101-200 (21.5%); 201-350 (14.2%); >350 (6.5%) Variables NR: symptomatic TB status, household TB contact, viral load, WHO HIV stage 	This retrospective cohort study involved analyzing data collected over 7 y from patients with TB in clinical programs. The study employed Cox proportional hazards regression to evaluate the association between changes in BMI category during the first month of TB treatment and subsequent mortality. Adjustments were made for potential confounders, including sex, age group, project site, and ART status as a time-dependent covariate.	The study included a total of 1090 new adult patients with TB who were HIV-positive, specifically focusing on those diagnosed with smear-negative and extrapulmonary TB. Data were drawn from 3 clinical programs across the mentioned countries.	The analysis revealed a robust association between changes in BMI category during the initial months of TB treatment and mortality outcomes. Patients who remained severely underweight or moved to a lower BMI category had aHR of 4.05 (95% CI 2.77-5.91, <i>P</i> <.001) for mortality compared to those who either maintained or moved to a higher BMI category. This indicates a significantly elevated risk of death associated with BMI category deterioration. Similarly, those who remained severely underweight or lost a BMI category showed over twice the rate of unfavorable TB treatment outcomes, with an aHR of 2.53 (95% CI 1.87-3.42). These findings underscore the importance of monitoring BMI changes in identifying individuals at heightened risk of mortality during TB treatment in HIV-positive populations [14]

^aWHO: World Health Organization.

^bCD4: cluster of differentiation 4.

^cART: antiretroviral therapy.

^dNR: not reported.

^eTB: tuberculosis.

^faHR: adjusted hazard ratio.

^gDR-TB: drug-resistant tuberculosis.

^hNote: Absolute frequencies (n) are reported alongside percentages where available. Variations in n values across categories reflect differences in reporting formats and sample denominators in the original studies included in this review.

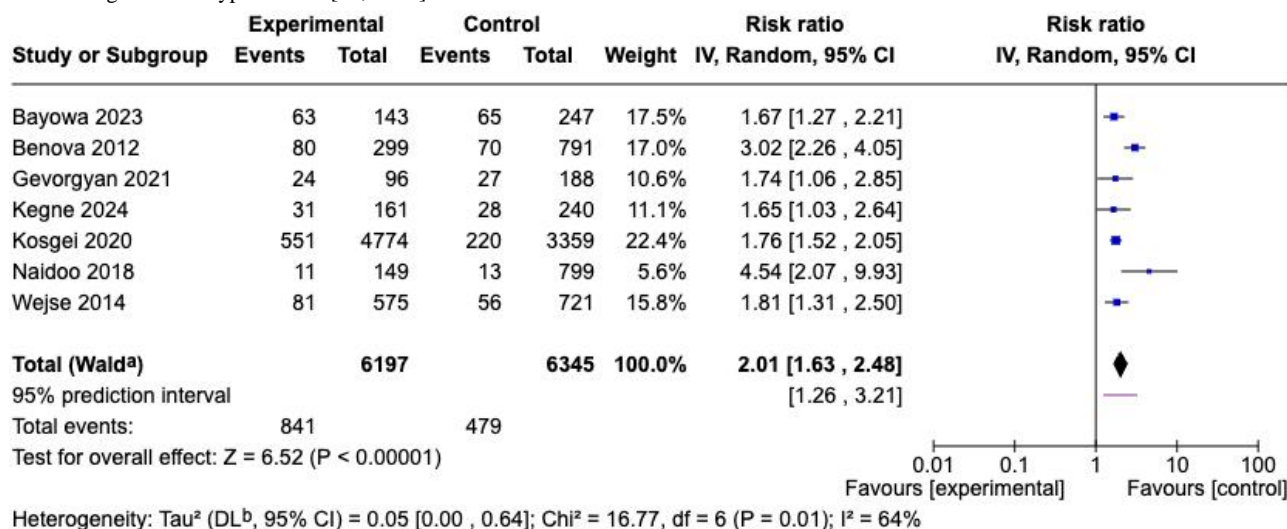
Meta-Analysis

In this study, the meta-analysis was conducted using Review Manager (RevMan) version 7.2, using the inverse-variance method under a random effects model to account for possible heterogeneity among the included studies [32]. This analytical approach assumes that the true effect size varies across studies due to differences in study design, populations, and settings, making it suitable for combining data from both Asian and African regions. The DerSimonian-Laird method was used to

estimate the between-study variance (τ^2), providing a more conservative and generalized pooled estimate [24].

Effect sizes were expressed as RR with corresponding 95% CI. Statistical heterogeneity was assessed using the *I*² statistic and Cochran *Q* (χ^2) test, which quantify the proportion of total variation across studies that is due to heterogeneity rather than chance [33]. Additionally, a 95% prediction interval was calculated to indicate the expected range of true effects in future studies conducted under similar conditions. The overall results of the meta-analysis are illustrated in the forest plot (Figure 2).

Figure 2. Forest plot of pooled meta-analysis showing the association between low BMI and mortality among patients with tuberculosis and HIV coinfection. The diamond represents the pooled risk ratio estimated using a random-effects model (DerSimonian and Laird method). The 95% CIs were calculated using the Wald-type method [14,26-31].



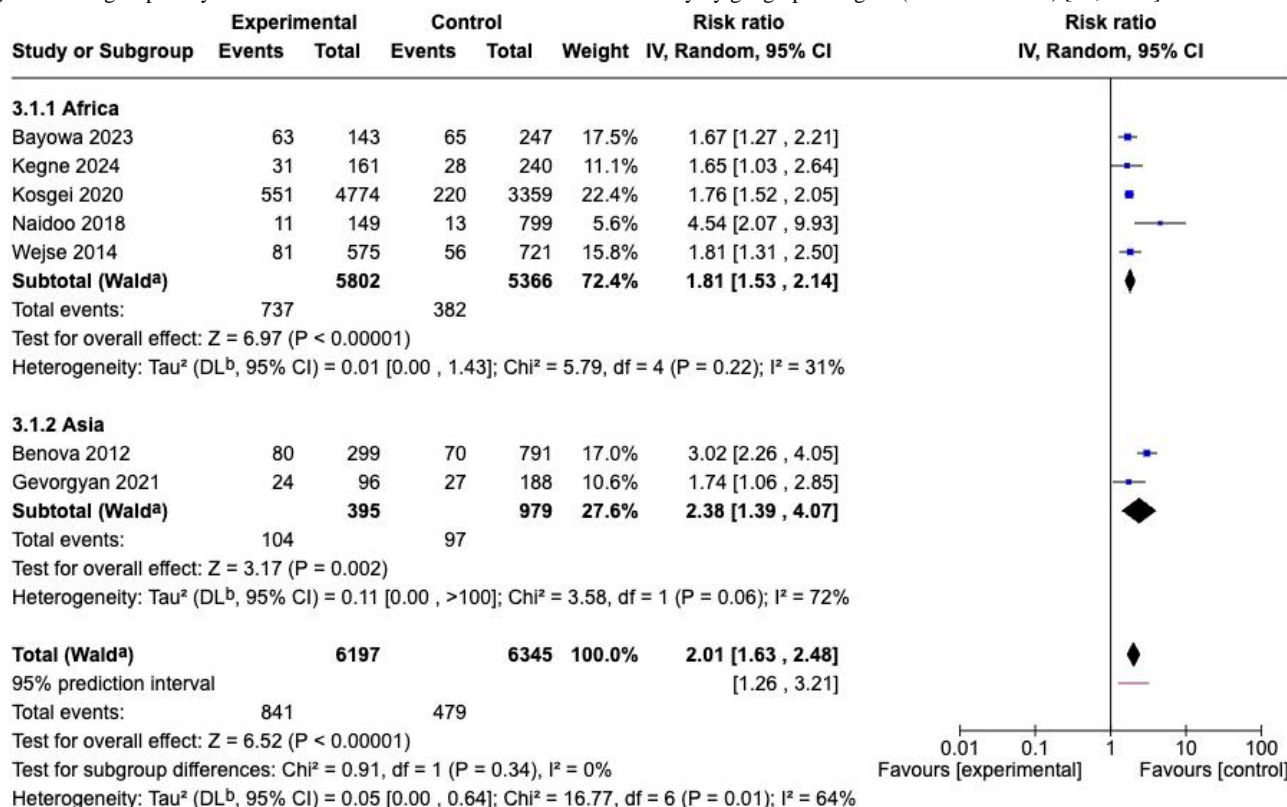
A total of 7 studies involving 12,734 participants (6197 in the low BMI group and 6345 in the normal BMI group) were included in the pooled analysis. The random effects meta-analysis revealed a significant association between low BMI (BMI < 18.5 kg/m²) and increased mortality among patients coinfecting with TB and HIV. The combined effect estimate indicated that individuals with low BMI had approximately twofold higher mortality risk compared to those with normal or higher BMI (RR=2.01; 95% CI 1.63 - 2.48; P<.001).

The overall heterogeneity among the included studies was moderate (I²=64%; P=.01), suggesting that the observed variation in effect sizes was not entirely due to chance. Such heterogeneity was acceptable in meta-analyses of observational studies, particularly given the differences in population characteristics, study design, and regional contexts (Africa and

Asia). The estimated between-study variance (τ²=0.05) also indicates that the heterogeneity was not excessive.

Further, a subgroup analysis by geographic region was conducted to explore potential sources of heterogeneity (Figure 3). The African subgroup yielded a pooled RR of 1.81 (95% CI 1.53 - 2.14; P<.001; I²=31%), indicating a stable and consistent association between low BMI and mortality with low heterogeneity. The Asian subgroup, meanwhile, showed a stronger pooled effect of RR=2.38 (95% CI 1.39 - 4.07; P=.002; I²=72%), reflecting greater variability likely due to smaller sample sizes and study-level differences. However, the test for subgroup differences (P=.34) revealed no statistically significant difference between the 2 regional estimates, implying that the detrimental effect of low BMI on survival was consistent across both continents.

Figure 3. Subgroup analysis of the association between low BMI and mortality by geographic region (Africa and Asia) [14,26-31].



These findings provided robust evidence that low BMI was a significant and consistent predictor of mortality among patients with TB and HIV coinfection in both Asia and Africa. The 95% prediction interval (1.26 - 3.21) further indicated that future studies conducted under similar conditions were expected to observe a harmful effect of low BMI on survival, even after accounting for between-study variability.

To ensure the robustness and internal validity of the pooled estimates presented in both the overall and subgroup analyses

(Figure 2), a risk of bias assessment was conducted for all included studies using the ROBINS-E tool. This step was crucial to evaluate potential methodological limitations that might have influenced the observed association between BMI and mortality among patients with TB and HIV coinfection. The detailed assessment across the 7 ROBINS-E domains is illustrated in Figure 4, while the overall summary of bias distribution is presented in Figure 5.

Figure 4. Risk of bias assessment by domain using the risk of bias in nonrandomized studies of exposures tool [14,26-31].

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Bayowa et al 2023	-	-	-	X	X	-	-	X
Benova et al 2012	X	-	X	-	X	+	-	X
Gevorgyan et al 2021	-	-	+	X	-	-	-	X
Kegne et al 2024	-	-	-	X	X	-	-	X
Kosgei et al 2020	-	-	-	X	-	-	-	X
Naidoo et al 2018	-	+	+	-	-	+	+	-
Wejse et al 2014	-	+	-	+	-	+	-	-

Domains:
 D1: Bias due to confounding.
 D2: Bias arising from measurement of the exposure.
 D3: Bias in selection of participants into the study (or into the analysis).
 D4: Bias due to post-exposure interventions.
 D5: Bias due to missing data.
 D6: Bias arising from measurement of the outcome.
 D7: Bias in selection of the reported result.

Judgement
 X High
 - Some concerns
 + Low

Figure 5. Summary of overall risk of bias distribution across included studies.

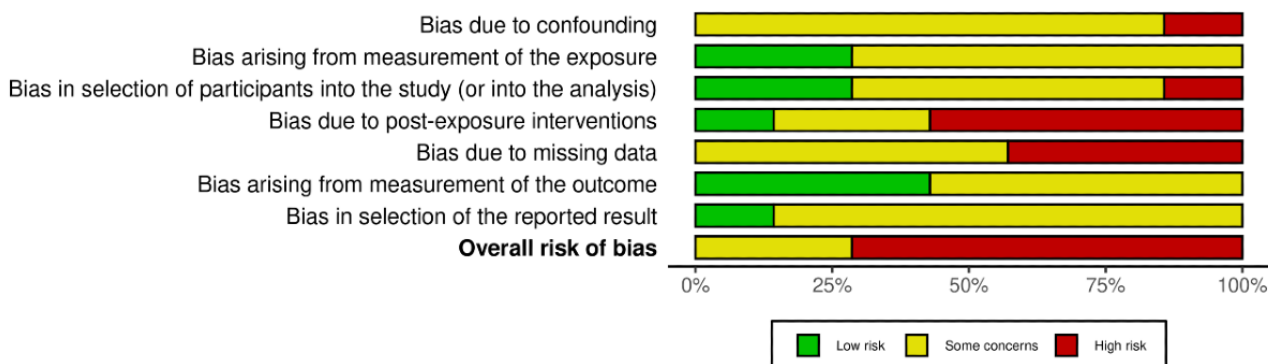


Figure 4 presents the domain-specific assessment of risk of bias for all included studies using the ROBINS-E tool. Most studies showed some concerns in several domains, particularly related to confounding (D1), postexposure interventions (D4), and missing data (D5). A few studies, Benova et al [14] and Kosgei et al [29], demonstrated high risk of bias in multiple domains, mainly due to incomplete adjustment for confounders and lack of clarity regarding data completeness. Conversely, Naidoo et al [30] and Wejse et al [31] exhibited relatively lower risk levels, particularly in domains concerning exposure and outcome measurement. Overall, these findings indicated that while some studies presented notable limitations, the collective evidence base remained methodologically sound for synthesis.

The aggregated distribution of bias levels presented in Figure 5 showed that approximately 60% - 70% of the included studies had some concerns, while a smaller proportion had high risk in at least 1 domain. Importantly, no study was classified as low risk overall, reflecting the inherent methodological limitations typical of observational designs. Despite the predominance of high-risk ratings, all studies were retained for quantitative synthesis because they contributed valuable information and

were consistent with the inclusion criteria. Furthermore, sensitivity analysis indicated that exclusion of high-risk studies did not substantially alter the direction of the pooled effect.

In summary, the synthesis of all ROBINS-E domains indicated that the evidence in this review was at moderate to high risk of bias. No studies met the criteria for low risk overall, reflecting the inherent methodological limitations of observational cohort studies in TB-HIV populations, including confounding factors, incomplete baseline information, and heterogeneity in clinical measurements. Nevertheless, the direction and magnitude of the effect estimates remained consistent across studies, and the pooled RR value showed stability in sensitivity analyses. These findings suggested that the association between low BMI and mortality remains strong and credible despite moderate to high risk of bias.

Discussion

Principal Findings

The present meta-analysis demonstrated a significant association between BMI and mortality among patients with TB and HIV

coinfection in Asia and Africa. The pooled estimate revealed that individuals with BMI less than 18.5 kg/m² had approximately twice the risk of death compared with those with normal BMI. This finding provides strong quantitative evidence that low BMI is an independent predictor of mortality in TB-HIV coinfecting populations. The direction and magnitude of this association remained consistent across subgroup analyses by region, further reinforcing the robustness of the effect.

These results corroborate previous observational and cohort studies that have consistently shown that better nutritional status improves survival outcomes in individuals with TB-HIV coinfection. Maintaining or improving BMI during treatment has been associated with faster clinical recovery, reduced incidence of opportunistic infections, and improved immune reconstitution. Conversely, undernutrition compromises immune function, increases susceptibility to severe disease progression, and reduces treatment tolerance, mechanisms that likely explain the higher mortality observed among patients with low BMI.

Subgroup analysis (Figure 3) demonstrated that the association between low BMI and increased mortality remained consistent across both regions, although the magnitude of risk was higher among African cohorts compared to those from Asia. This may reflect regional differences in baseline nutritional status, ART coverage, and health care infrastructure. In Africa, a higher prevalence of advanced immunosuppression at TB or ART initiation and limited access to nutritional support programs likely amplify the impact of malnutrition on mortality. Conversely, in Asian settings, although the overall BMI distribution tends to be higher, undernutrition still poses a significant mortality risk among individuals with HIV-associated wasting and late TB presentation. These findings reinforce the universality of BMI as a prognostic marker, regardless of regional or demographic variation.

For instance, a study in South Africa reported that HIV-infected individuals with a BMI less than or equal to 18.5 experienced significantly higher mortality rates compared to those with a BMI more than 30 kg/m², with corresponding rates of 10.4 and 1.6 per 100 person-years, respectively [34]. Similarly, Yen et al [15] found that patients with TB with a BMI less than 18.5 kg/m² exhibited significantly increased risks of all-cause mortality with adjusted odds ratio (aOR) 1.66, TB-specific mortality (aOR 2.14), and non-TB mortality (aOR 1.58) [15]. Further supporting evidence is provided by studies conducted in Myanmar and Zimbabwe, which demonstrated that remaining severely underweight or experiencing a decline in BMI during the first month of TB treatment significantly increased mortality among HIV-positive patients with smear-negative and extrapulmonary TB [14]. Conversely, in the same South African cohort, overweight and obese HIV-infected individuals had notably lower mortality risks, with adjusted hazard ratios of 0.59 and 0.48, respectively, compared to those with normal BMI [34]. These findings underscore the prognostic value of BMI as an indicator of clinical outcomes in this population.

Malnutrition appears to be a major risk factor contributing to elevated mortality in patients with TB-HIV coinfection. In Taiwan, Lai et al [12] reported that patients with TB with poor nutritional status had a 2.22-fold higher risk of early death within

the first 8 weeks of treatment [12]. Likewise, in sub-Saharan Africa, Koethe et al [35] found that low baseline BMI at ART initiation was a robust predictor of early mortality among HIV-infected adults [35].

Several biological and clinical mechanisms may underlie the observed association between BMI and mortality. Low BMI often reflects underlying malnutrition, compromising immune function, including reduced CD4 lymphocyte counts. A CD4 count less than 200 cells/mm³ is widely recognized as a critical threshold of severe immunosuppression, associated with heightened vulnerability to opportunistic infections and increased mortality [36,37]. Additionally, a high HIV viral load (>100,000 copies/mL) reflects impaired immune control and has been linked to increased incidence of TB and mortality risk.

Beyond immunosuppression, malnutrition may exacerbate systemic inflammation. Individuals with low BMI often display a proinflammatory state, characterized by hypercoagulability, endothelial activation, and the development of disseminated intravascular coagulation, a complication associated with poor clinical outcomes [37]. Elevated levels of proinflammatory cytokines and related biomarkers have also been observed in patients with TB and HIV coinfection. They may contribute to tissue damage and multiorgan failure, further elevating the risk of death [38].

In contrast, a higher BMI may provide metabolic and energy reserves that help mitigate the physiological stress of chronic infection. Nutritional status has also been shown to influence treatment efficacy; malnutrition may delay therapeutic response, prolong hospitalization, and worsen overall prognosis [39]. Therefore, comprehensive and individualized nutritional assessments are essential for optimizing treatment outcomes [40]. Furthermore, interactions between food and medications may modulate treatment effectiveness or side effect profiles, reinforcing the bidirectional relationship between nutritional status and treatment success [41].

Clinical and Public Health Implications

The implications of these findings are substantial for public health strategies. Given the consistent association between low BMI and increased mortality, nutritional interventions should be considered a fundamental component of TB-HIV management protocols. Timely nutritional support—such as the provision of food supplements and access to nutrient-rich diets—alongside early diagnosis may significantly improve clinical outcomes [42,43]. Community-based strategies that incorporate routine nutritional monitoring and adherence support also have great potential to improve survival rates in this population. Evidence shows that food insecurity is a major barrier to adherence in both HIV and TB care, while food baskets and nutritional supplements have been shown to improve treatment adherence and completion [44]. Integrating systematic BMI checks and early assessment of malnutrition risk into routine TB-HIV service delivery will ensure that high-risk patients are identified quickly and that nutritional support is provided as part of standard care, rather than as an additional service.

A coordinated approach linking nutritional rehabilitation with ART initiation and directly observed therapy, short course (DOTS), can further strengthen treatment outcomes. Patients living with TB-HIV who are malnourished often begin therapy with advanced immunosuppression and high vulnerability to early mortality, making nutritional management synchronized with pharmacological therapy crucial. This is particularly important because food insecurity has been shown to worsen ART side effects and reduce adherence when medications are taken without sufficient food [44]. Developing operational guidelines that clearly integrate nutritional support into ART and TB treatment service flows can encourage more consistent and effective implementation across health care facilities.

Finally, at the policy and health system level, integrating structured nutrition services into national TB and HIV guidelines—accompanied by program budget adjustments to maintain food supplementation packages—will be key to long-term sustainability. Strengthening the supply chain for nutrition commodities and including nutrition-related indicators in routine TB-HIV monitoring and evaluation systems can further improve service continuity. These measures offer a viable and sustainable integrated approach to improving TB-HIV coinfection management outcomes in high-burden regions of Asia and Africa, while emphasizing the importance of institutionalizing nutrition-based interventions in the context of resource-constrained health services.

Conclusion and Recommendations

This systematic review and meta-analysis confirm that low BMI ($<18.5 \text{ kg/m}^2$) is a strong and independent predictor of mortality among patients coinfecting with TB and HIV in Asia and Africa. The pooled estimate (RR=2.01; 95% CI 1.63 - 2.48) indicates that individuals with BMI less than 18.5 kg/m^2 experience approximately twofold higher mortality risk compared to those with normal BMI. This finding reinforces the critical prognostic role of nutritional status in TB-HIV comanagement. Although moderate heterogeneity ($I^2=64\%$) and variations in study quality were observed, the association between low BMI and increased mortality remained consistent and statistically robust across subgroup analyses.

These findings reaffirm that nutrition forms a cornerstone—not an adjunct—of TB-HIV clinical management. Given the two-fold increase in mortality risk observed among underweight patients, integrating nutritional assessment, intervention, and routine BMI monitoring into TB and HIV programs is essential

to improve survival outcomes. National health systems in Asia and Africa should prioritize early nutritional screening and timely supplementation, particularly for underweight patients and those initiating ART. Furthermore, policy frameworks should promote the integration of TB, HIV, and nutrition services through intersectoral collaboration. Future studies and policy evaluations should assess the effectiveness of structured nutrition-ART interventions and explore context-specific BMI thresholds for predicting mortality and enhancing long-term treatment success among TB-HIV coinfecting populations.

Limitations

Several limitations should be considered when interpreting these findings. First, only 7 cohort studies met the inclusion criteria, which may have limited the generalizability of findings to broader TB-HIV populations across diverse clinical settings and precluded stratified analyses (eg, by sex, ART status, or CD4 count). This reflects the scarcity of prospective studies assessing mortality outcomes among TB-HIV coinfecting populations in Asia and Africa. Second, substantial heterogeneity ($I^2=64\%$) was observed, likely arising from differences in study design, clinical settings, ART coverage, and the operational definition of BMI and mortality. Third, variation in BMI categorization and timing of measurement across studies may have introduced misclassification bias. Fourth, although cohort designs support temporal inference, residual confounding remains possible, as critical covariates, such as CD4 cell count, viral load, ART adherence, socioeconomic factors, and comorbidities, were inconsistently reported, potentially leading to residual confounding in the pooled estimates. Additionally, none of the included studies reported symptomatic versus asymptomatic TB status, preventing further stratified analyses based on this clinically important variable. Finally, restricting inclusion to English-language publications may have led to language bias and underrepresentation of studies published in local Asian or African journals.

Despite these limitations, this meta-analysis provides robust and consistent evidence that BMI serves as a clinically relevant and modifiable predictor of mortality in patients with TB and HIV coinfection. Strengthening integrated nutritional and clinical care, along with context-specific program implementation, is therefore vital to reduce preventable deaths and to achieve the global End TB and United Nations Programme on HIV/AIDS 95-95-95 targets.

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Artificial intelligence tools (ChatGPT) were used during the writing process to improve the readability and language quality of this manuscript. The author affirms full responsibility for the content and interpretation presented.

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Data Availability

All data analyzed during this study are included in this published article.

Authors' Contributions

MASMI and TYMW were responsible for developing the protocol. They were involved in various aspects of the study, including designing the study, selecting the eligible studies, extracting data, performing statistical analyses, drafting the initial versions, and revising the manuscript. PNCI, WWL, and LAN edited the final draft of the manuscript, which was subsequently read and approved by the first and second authors.

Conflicts of Interest

None declared.

Checklist 1

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.

[[DOCX File, 32 KB](#) - [apinj_v10i1e81905_app1.docx](#)]

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Abbreviations

aOR: adjusted odds ratio

ART: antiretroviral therapy

CD4: cluster of differentiation 4

MeSH: Medical Subject Heading

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol

ROBINS-E: Risk of Bias in Non-Randomized Studies – of Exposure

RR: risk ratio

TB: tuberculosis

WHO: World Health Organization

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Complementary Therapies for Diabetic Foot Ulcer Healing Among Patients in Asia: Scoping Review

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Abstract

Background: Diabetic foot ulcers (DFUs) are a severe complication of diabetes mellitus that can lead to amputation and mortality. Conventional treatments may be insufficient, leading to an interest in complementary therapies such as herbal medicine, acupuncture, maggot debridement therapy, and biological therapies. These approaches are widely used in Asia, yet their effectiveness and integration into clinical practice remain underexplored.

Objective: The scoping review aimed to map the types of complementary therapies used for DFU healing in Asia and evaluate their reported effectiveness, implementation challenges, and opportunities for integration into conventional care.

Methods: A scoping review was conducted using the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Reviews) framework and the methodology of Arksey and O'Malley. Articles were sourced from the PubMed, Scopus, and ProQuest databases, covering studies published from 2014 to 2024. The population, concept, and context model guided the selection of studies, focusing on patients with DFUs, complementary therapies, and the Asian region.

Results: Eight studies met the inclusion criteria. The most commonly used therapies included herbal treatments (eg, traditional Chinese medicinal foot soaks and *Teucrium polium*), biological therapies, including maggot debridement therapy and platelet-rich fibrin with hyaluronic acid, physical therapy (acupuncture), and psychological therapies (music therapy). Topical *T polium* significantly reduced wound size, and platelet-rich fibrin combined with hyaluronic acid increased vascular endothelial growth factor levels while reducing inflammation. Music therapy lowered the diabetes-related distress score. Despite these promising results, challenges remain, including a limited number of large-scale randomized controlled trials, regulatory barriers, and cultural perceptions affecting therapy acceptance.

Conclusions: Complementary therapies are promising adjuncts for DFU management in Asia, where traditional medical practices are prevalent. Multidisciplinary collaboration between health care providers, policymakers, and traditional practitioners is essential for safe and effective integration. Further well-designed randomized controlled trials are required to confirm the efficacy of these therapies and inform evidence-based policies.

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KEYWORDS

diabetic foot ulcer; complementary therapies; wound healing; Asia; PRISMA; Preferred Reporting Items for Systematic reviews and Meta-Analyses

Introduction

Diabetic foot ulcers (DFUs) are a severe complication of diabetes mellitus that can have significant health consequences, including amputation and increased mortality. Their highly complex pathophysiology involves a combination of ischemic neuropathy and infection, which hinders wound healing. Furthermore, prolonged hyperglycemia, hypertension, and hyperlipidemia contribute to oxidative stress and impaired blood flow, making DFUs particularly challenging to heal [1]. The lifetime incidence of foot ulceration among people with diabetes is estimated at 19% to 34%, and this burden is projected to

increase due to longer survival and more complex comorbid conditions [2]. A systematic review estimated the global prevalence of DFUs to be approximately 6.3%, while a local study in Pakistan reported a prevalence of 16% among patients with diabetes [3]. Moreover, DFUs are associated with an increased risk of lower-extremity amputation and higher mortality, particularly among older adults and individuals with comorbid conditions [4]. Given the high prevalence and serious complications of DFUs, a comprehensive treatment approach is essential. In addition to conventional medical therapy, various adjunctive interventions have been developed to support wound healing, including complementary therapies, which have garnered increasing attention in the management of DFUs.

The integration of complementary therapy in the management of DFUs in Asia faces various challenges that may affect its effectiveness and acceptance, one of which is a lack of understanding and knowledge about complementary therapies among patients and health care professionals. In recent years, the incorporation of complementary therapy into DFU management has gained increasing attention, as these approaches can be used alongside conventional medical treatments and improve patient outcomes [5]. Traditional medicine plays a significant role in DFU management in Asia, with traditional Chinese medicine (TCM) and Ayurveda being widely practiced. These approaches have been shown to offer benefits in wound healing and infection control through herbal medicine, acupuncture, and dietary modifications to accelerate the healing process and restore balance to the body [6]. Recent studies have indicated that specific TCM formulations, such as *shengji* ointment, can significantly enhance the healing rate of DFUs, highlighting the potential for integrating these therapies into conventional treatment protocols [7]. Similarly, Ayurvedic practices have been reported to reduce infection rates and improve the overall quality of life of patients with DFUs [8]. Despite the promise of complementary therapies to support DFU healing, challenges remain in their integration into clinical practice. Therefore, further research and evidence-based approaches are necessary to ensure the safety, efficacy, and acceptance of these therapies for the holistic management of DFUs.

Complementary therapy is essential for health care management, including in the context of patients with DFUs in Asia. Research indicates that although many patients are interested in complementary therapy, they often lack adequate information regarding its effectiveness and safety [9]. Complementary therapies such as acupressure and massage effectively reduce pain and improve patient quality of life; however, many individuals remain uncertain about integrating these therapies with conventional medical treatments [10]. A study revealed that among 653 patients with DFUs, 21.7% used topical alternative treatments, while 31.2% combined conventional and alternative therapies [11]. This trend underscores the importance of health care providers being aware of various treatment modalities that patients may use to complement standard medical care. The efficacy of some complementary therapies has been documented in recent literature, such as ozone therapy, which has shown promising results in DFU healing, as evidenced by case reports highlighting its success in high-risk patients [12]. As the number of patients using complementary therapy in DFU management continues to increase, a more inclusive and evidence-based approach is necessary to integrate these therapies into clinical practice. Collaboration between health care professionals and complementary therapy practitioners is crucial to ensure that patients receive maximum benefits safely and effectively.

Complementary therapy in Asia for DFU healing has increased patient interest in alternative treatments rooted in local medical traditions. However, challenges regarding regulation, education, and integration with conventional medical care remain. Past findings highlight the importance of nutritional factors in DFU healing, which may encourage patients to seek nutrition-based

complementary therapies aligned with their traditional medical practices [13]. In addition, the frequency of DFUs among patients with diabetes underscores the need for a multidisciplinary approach that incorporates complementary therapy despite existing integration barriers [14]. A study examining DFU prevalence in Ethiopia highlighted the importance of health education in improving patients' understanding of foot care, which may incorporate complementary therapies rooted in local practices [15]. Although this study focuses on therapies delivered by nurses in person, it is also important to note that digitalized approaches to complementary therapies are now emerging. The use of apps based on TCM and mind-body practices has become a popular alternative, expanding the reach of these therapies to patients accessing health services via mobile devices [16]. However, to date, no studies have specifically examined the effectiveness of complementary therapy for DFU healing in Asia. The question remains as to how effective complementary therapies are for promoting healing of DFUs in this region. Therefore, the primary aim of this scoping review was to map the types of complementary therapies applied to DFU healing in Asia. The secondary aim was to evaluate their reported effectiveness and identify the challenges and opportunities for integration into clinical practice.

Methods

We conducted a scoping review based on the PRISMA-Scr (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Reviews) guidelines [17] to collect and summarize the literature on complementary therapies for DFU healing in Asia.

The methodology used in this review followed the 5-stage framework developed by Arksey and O'Malley [18]. This approach maps the available literature, identifies research gaps, and provides a comprehensive overview of the existing evidence. The methodological stages applied in this review include stage 1, formulating the research question; stage 2, identifying relevant studies; stage 3, selecting studies for inclusion in the review; stage 4, charting data from the selected studies; and stage 5, analyzing, synthesizing, and reporting the findings.

Stage 1: Research Question

The research question in this review is as follows: How effective are complementary therapies in promoting the healing of DFUs in Asia?

Stage 2: Relevant Studies and Search Strategy

This review focuses on complementary therapies for DFU. A comprehensive literature search was conducted across PubMed, Scopus, and ProQuest databases between May and September 2023. To ensure the inclusion of the most recent evidence, the search was updated on January 18, 2025. The search was restricted to full-text articles published in English between January 2014 and December 2024, in accordance with the predefined 10-year review period. The search strategy used Medical Subject Headings terms and relevant Boolean operators, adapted for each database. Detailed search strings for all databases are provided in [Multimedia Appendix 1](#).

Stage 3: Study Selection

Studies were screened based on predefined inclusion and exclusion criteria (Multimedia Appendix 2) in accordance with PRISMA-ScR guidelines [17]. All records were managed in Rayyan AI (Rayyan Systems, Inc) [19]. Duplicates were removed before title, abstract, and full-text screening.

Stage 4: Data Extraction

Data were extracted to obtain key information from journal articles relevant to the research topic, including authors' names and publication years, titles, research objectives, study methods, findings, and conclusions. This step aimed to facilitate the extraction of essential data required for the synthesis of the study.

Stage 5: Thematic Summary and Key Findings

The literature findings were used to identify the results based on emerging keywords. This review analyzed all articles based

on their titles, abstracts, and full texts, followed by a thorough examination. All analyzed articles contained information regarding complementary therapies for DFU healing in Asia.

Ethical Considerations

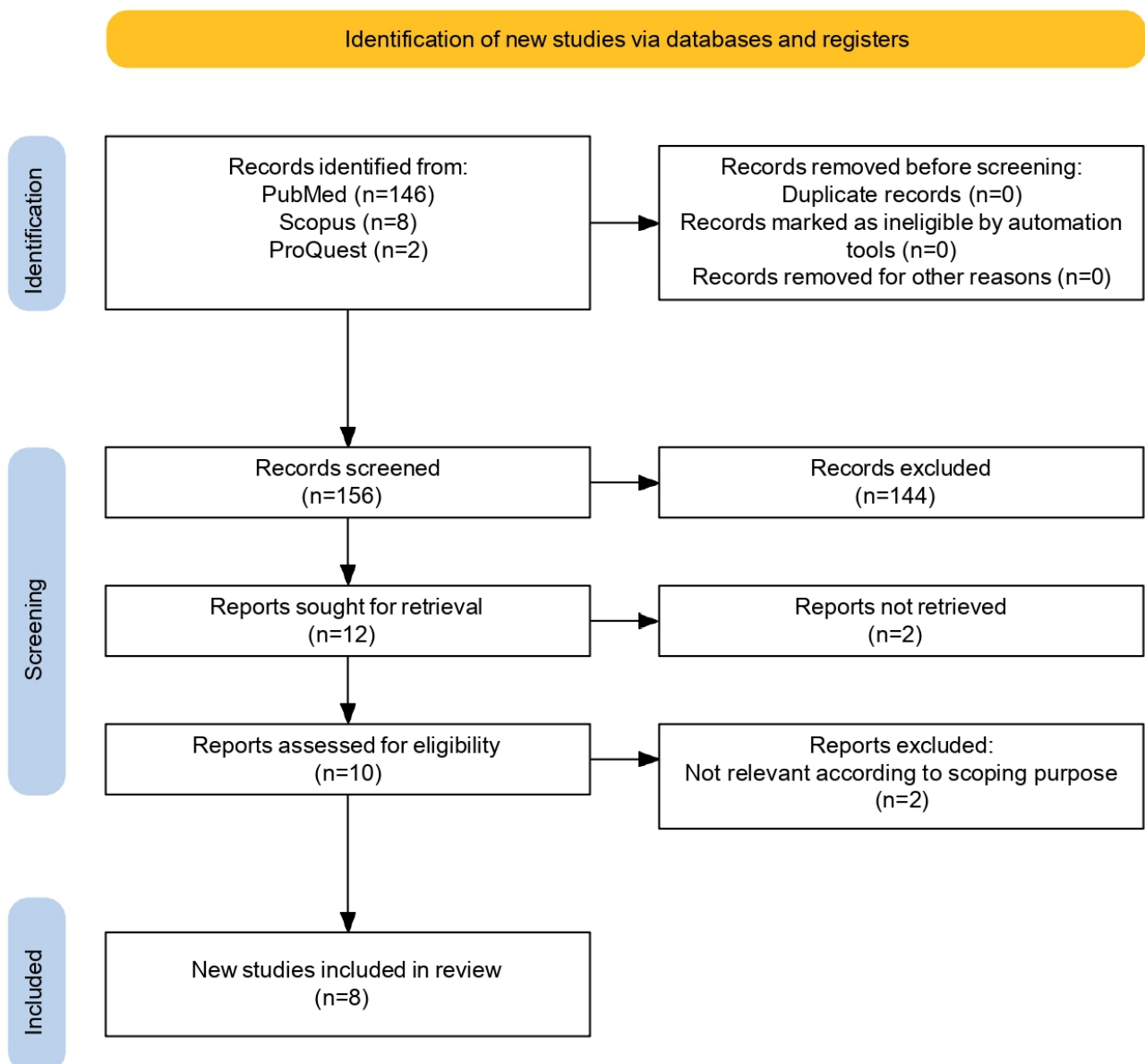
This study was declared exempt by the institutional review board of Universitas Hasanuddin, as the analyzed articles only contained anonymized information or did not include any personally identifiable information.

Results

Effectiveness of Complementary Therapies

The review included a final total of 8 studies [6,20-26] (Figure 1). Several interventions demonstrated potential benefits for DFU management.

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Reviews) flow diagram of the study selection process.



Herbal Therapies

A randomized controlled trial (RCT) on *Teucrium polium* ointment showed significantly greater wound size reduction and higher complete healing rates compared with placebo, with no notable adverse effects [22]. Another RCT protocol investigating a herbal foot bath decoction aims to evaluate its effects on inflammatory cytokines, including interleukin-6, as well as clinical outcomes in patients with diabetic peripheral neuropathy. [6].

Biological Therapies

Maggot debridement therapy (MDT) significantly increased microRNA-126 expression, enhancing angiogenesis and wound healing [21]. Similarly, the combination of advanced platelet-rich fibrin and hyaluronic acid resulted in higher vascular endothelial growth factor expression and lower interleukin-6 levels, indicating improved angiogenesis and reduced inflammation [26].

Psychological Therapies

A quasi-experimental study of music therapy found significant reductions in distress levels among patients with DFUs, highlighting the potential role of psychological interventions in improving patient well-being [25], which may ultimately facilitate the healing process for DFUs.

Sociocultural Factors and Complementary and Alternative Medicine

Patterns of complementary and alternative medicine use were reported in both Indonesia and Thailand. In Indonesia, 54.3% of patients with type 2 diabetes used complementary and alternative medicine, with herbal medicine (100%), spiritual healing (68.3%), and massage (42.3%) being the most common, often recommended by family members. Key determinants included affordability, perceived safety, and cultural beliefs [20]. In Thailand, complementary and alternative medicine use was more prevalent among women and farmers, reflecting sociodemographic influences [23]. A qualitative study in rural

China further revealed that traditional beliefs, limited access to health care services, and high treatment costs were significant barriers to timely medical care-seeking for DFUs [24]. These findings highlight the role of socioeconomic and cultural factors in shaping health behaviors and care choices among Asian populations with diabetes. In addition, DFUs impose a substantial economic burden in the region: in Iran, the economic impact was estimated at US \$8.7 to \$35 billion, representing 0.6% to 2.4% of the national GDP, whereas in Indonesia, in-hospital treatment costs for DFUs were Rp 65 million per episode (approximately US \$3800), posing a considerable financial strain on patients and families [27,28].

Study Characteristics, Implementation Challenges, and Emerging Models

The included studies were conducted across several Asian countries: 2 in Indonesia [20,26], 3 in China [6,21,24], and 1 each in India [25], Thailand [23], and Iran [22], as illustrated in Figure 2. Settings varied, with most studies conducted in hospitals (n=3) [21,22,26], followed by primary health care centers (n=1) [23] and traditional hospitals (n=1) [6], as well as at a tertiary hospital (n=1) [25] and in rural communities (n=2) [20,24]. Study designs included 3 RCTs [6,22,26], 2 cross-sectional surveys [20,23], 1 quasi-experimental studies [25], 1 experimental (pre-post clinical study) [21] and 1 qualitative study [24]. Sample sizes ranged from 15 participants (in a qualitative study) to 628 participants (in a cross-sectional survey).

The key characteristics of the included studies are summarized in a synthesis grid (Table 1). Despite promising findings, the studies highlighted challenges in integrating complementary therapies into DFU management. These included small sample sizes, limited standardization of interventions, and variability across health care settings. At the same time, emerging models such as nurse-led telehealth and mobile health interventions showed potential for enhancing patient education and self-care practices. However, their clinical effectiveness in DFU outcomes requires further validation.

Figure 2. Geographic distribution of included studies on complementary and alternative therapies for diabetes and diabetic foot ulcers across Asia. Map generated using MapChart (Minas Giannekas) [29].



Table . Synthesis grid of included studies.

Authors (year)	Country	Study design	Sample size, n	Intervention/therapy	Main outcomes
Fan et al [6] (2018)	China	Randomized controlled trial	640	Foot bath decoction and placebo foot bath (traditional Chinese medicine)	Primary outcome: change in Toronto Clinical Scoring System score. Secondary outcomes: nerve conduction velocity, blood glucose (fasting blood glucose, postprandial blood glucose, hemoglobin a _{1c}), blood lipids (total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein), inflammatory cytokines (tumor necrosis factor- α , interleukin-6, C-reactive protein), quality of life (EQ-5D), and traditional Chinese medicine symptom scores.
Sari et al [20] (2021)	Indonesia	Cross-sectional	628	Assessment of self-reported CAM ^a use (herbal medicine, spiritual practices, massage, honey)	CAM use: 54.3% (herbal 100%, spiritual 68.3%, massage 42.3%); predictors: affordability (OR ^b 4.59, 95% CI 3.01 - 7.01), safety (OR 2.04), perceived effectiveness (OR 1.75).
Zhang et al [21] (2017)	China	Experimental (pre-post clinical study)	60	MDT ^c	Patients with diabetic foot ulcers had significantly lower microRNA-126 levels compared with patients without them ($P=.001$). Following MDT, microRNA-126 levels significantly increased ($P=.04$).
Fallah Huseini et al [22] (2024)	Iran	Randomized controlled trial	70	<i>Teucrium polium</i> ointment	Wound size decreased significantly from 3.52 (SD 1.47) cm ² to 0.717 (SD 0.19) cm ² in the intervention group, compared with a reduction from 3.21 (SD 1.67) cm ² to 1.63 (SD 0.72) cm ² in the placebo group ($P=.0001$). Complete wound healing was achieved in 51.7% of patients in the intervention group versus 15.4% in the placebo group ($P=.001$).
Wanchai and Phrompayak [23] (2016)	Thailand	Cross-sectional	508	Self-reported use of CAM	CAM use was higher in women ($P=.02$) and farmers ($P=.007$).

Authors (year)	Country	Study design	Sample size, n	Intervention/therapy	Main outcomes
Zhu et al [24] (2024)	China	Qualitative (interviews)	15	Exploration of sociocultural factors influencing wound care-seeking behavior	Barriers included traditional beliefs, limited access, and high treatment costs.
Ullas et al [25] (2023)	India	Quasi-experimental	30	Music therapy intervention	The distress score significantly decreased, from 3.7 (SD 0.6) at baseline to 2.4 (SD 0.2) after the intervention ($P=.04$).
Kartika et al [26] (2021)	Indonesia	Randomized controlled trial	30	Advanced platelet-rich fibrin combined with hyaluronic acid	Vascular endothelial growth factor levels increased significantly on day 3 ($P=.003$) and day 7 ($P<.001$), while interleukin-6 levels decreased significantly on day 7 ($P=.02$).

^aCAM: complementary and alternative medicine.

^bOR: odds ratio.

^cMDT: maggot debridement therapy.

Discussion

Effectiveness of Complementary Therapies

Our scoping review highlights the potential role of complementary therapies in DFU management, including herbal interventions such as TCM foot bath decoction [6] and *Teucrium polium* [22], demonstrated anti-inflammatory and pro-angiogenic properties, consistent with their use in Asian traditional medicine practices [6,21,26]. Despite encouraging results, most studies were limited by small sample sizes, inadequate randomization, and a lack of standardized dosages, reducing the generalizability of findings. Biological therapies, including MDT and platelet-rich fibrin combined with hyaluronic acid, also showed promising effects in enhancing angiogenesis and reducing inflammation. However, evidence remains inconsistent across studies, with some RCTs questioning the superiority of MDT over standard care [21]. These findings underscore the need for rigorously designed clinical trials to establish safety, efficacy, and standardized protocols for complementary therapies in DFU care.

Sociocultural and Economic Context in Asia

Sociocultural and economic contexts strongly influence treatment-seeking behaviors and the adoption of complementary and alternative medicine in Asia. In Indonesia and Thailand, complementary and alternative medicine use is widespread among patients with diabetes, primarily driven by affordability, cultural beliefs, and family influence [20,23,30]. In rural China, traditional beliefs, limited access to health care services, and high treatment costs were reported as significant barriers to timely DFU care [24]. These patterns reflect broader socioeconomic challenges in many Asian countries, where limited insurance coverage and high out-of-pocket costs make conventional DFU treatments less accessible. Consequently, patients often turn to complementary and alternative medicine as a perceived affordable and culturally acceptable alternative.

Addressing these structural factors is essential to improving equity in DFU management and to ensuring that evidence-based complementary therapies are safely integrated into clinical practice.

Holistic and Emerging Models of Care

Psychological and digital health interventions offer additional opportunities to complement medical and surgical approaches to DFU care. Music therapy, for example, was associated with significant reductions in diabetes-related distress, which may improve adherence to wound care and overall patient well-being [25]. Evidence from external studies also suggests that mindfulness and other behavioral interventions may enhance glycemic control and reduce distress, although their direct impact on DFU healing remains unclear [31]. Emerging models, including mobile health apps and nurse-led telehealth programs, have demonstrated feasibility in improving patient education, self-care practices, and remote consultation [30,32]. While clinical outcomes have not been consistently reported, these approaches highlight the potential for integrating psychological support and digital health innovations into holistic DFU management, particularly in resource-limited settings.

Opportunities and Implications for DFU Management

Long-term clinical trials are necessary to assess the sustained effects of complementary therapies on wound healing and patient quality of life. Future studies should also explore the underlying biological mechanisms of herbal interventions to understand their therapeutic potential [22]. Investigating combined approaches, such as platelet-rich fibrin, hyaluronic acid, and antibiotics, may offer integrative treatment pathways for DFUs [26]. Collaboration between conventional clinicians and complementary therapy practitioners is vital to ensure evidence-based, safe, and practical implementation [20]. Additionally, enhancing patient education and public awareness about the realistic benefits and limitations of these therapies can promote more informed decision-making.

Evaluation of Cost-Effectiveness

Economic evaluations of complementary therapies are required to compare their cost-effectiveness with that of conventional treatments. For instance, assessing the cost-benefit ratio of acupuncture for improving glycemic control or comparing MDT with antibiotic therapy in preventing amputations may help justify their integration into standard care [33,34]. Such analyses would provide valuable insights into the feasibility and scalability of incorporating complementary therapies into national health care systems.

Recommendations

Future research is recommended to further investigate the effectiveness, biological mechanisms, and integration of complementary therapies in managing diabetes mellitus and DFUs. One critical direction for future studies involves conducting long-term clinical trials to evaluate the sustained effects of complementary therapies with a minimum follow-up period of 6 months or longer. This would provide a comprehensive understanding of their impact on wound healing, blood glucose control, and patient quality of life.

Qualitative studies of patients' perceptions of complementary therapies are also important from social and cultural perspectives. Many patients with diabetes, particularly those in rural communities, tend to prefer traditional therapies to conventional medical treatments. Therefore, exploratory research should investigate the social, economic, and cultural factors that influence patients' decisions to use complementary therapies. This can provide valuable insights into the factors driving therapeutic choices and contribute to the development of culturally sensitive health care interventions.

Lastly, cost-effectiveness studies of complementary therapies are necessary to compare their financial and therapeutic benefits with those of conventional treatments. Future research is expected to provide more robust scientific evidence regarding the efficacy, safety, and integration of complementary therapies for the management of diabetes and DFUs. This evidence-based approach will support the incorporation of complementary therapies into holistic and patient-centered care strategies, ultimately benefiting patients and the health care system.

Critical Appraisal of Included Studies

Although we did not perform a critical appraisal because it is not mandatory in a scoping review, we observed that several included studies had limitations in study design. These included

small sample sizes, a lack of randomization or blinding, and an absence of standardized outcome measures. The heterogeneity of study designs, ranging from case reports to quasi-experimental studies and RCTs, complicates the interpretation and generalization of our results. These limitations suggest that while the findings are promising, they should be interpreted cautiously and validated through further high-quality research.

Opportunities and Implications

The integration of complementary therapies into clinical DFU care in Asia faces multiple barriers, as reflected by the studies included in this review. Regulatory frameworks for traditional and complementary therapies vary widely across countries, and are often incomplete or inconsistent, resulting in limited institutional support and ambiguous clinical guidelines. Furthermore, a lack of formal education and training for health care providers in evidence-based complementary practices contributes to uncertainty and resistance to implementation. Cultural perceptions also play a role, with some clinicians and patients viewing such therapies as informal or unscientific despite their profound historical and cultural relevance.

Study Limitations

Although this scoping review indicates the potential of complementary therapies to support the healing of DFUs, there are several limitations in the current body of research. These limitations include a lack of long-term evidence and standardized therapeutic protocols, as well as challenges in integrating complementary therapies with conventional treatments. Therefore, further research using more rigorous clinical trial designs with larger sample sizes and comprehensive cost-effectiveness evaluations is warranted to ensure the safety and efficacy of complementary therapies in DFU management.

Conclusion

Complementary therapies have significant potential for supporting the healing of DFUs in Asia; however, further research is necessary to confirm their efficacy and safety. Integrating complementary therapies into DFU management requires an evidence-based approach, more transparent regulatory frameworks, and comprehensive education for both health care providers and patients. With a thorough and evidence-based approach, complementary therapies can become part of a more holistic DFU treatment strategy, contributing to improved clinical outcomes and reducing the economic burden associated with diabetes complications.

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Authors' Contributions

ADMYP contributed to the study conceptualization, methodology, data analysis, and drafting of the manuscript. SY contributed to data screening, data extraction, and critical revision of the manuscript. HB and MJT contributed to manuscript review. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Summary of literature search strategy—databases, keywords, and selection results.

[[DOCX File, 17 KB - apinj_v10i1e76301_app1.docx](#)]

Multimedia Appendix 2

Problem, concept, and context framework.

[[DOCX File, 14 KB - apinj_v10i1e76301_app2.docx](#)]

Checklist 1

PRISMA-ScR Checklist.

[[PDF File, 190 KB - apinj_v10i1e76301_app3.pdf](#)]

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Abbreviations

DFU: diabetic foot ulcer

MDT: maggot debridement therapy

PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Reviews

RCT: randomized controlled trial

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Breast Health Education as a Motivator for Breast Self-Examination Practice in High-Risk Women: Grounded Theory Analysis

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Abstract

Background: Women in low-resource regions face a higher risk of breast cancer. Implementing a breast health initiative that promotes breast self-examination practice could aid in the early detection and prevention of breast cancer complications.

Objective: This study aimed to explore and comprehend the experiences of high-risk women, focusing on their breast self-examination practice and the factors that influence their effectiveness in managing breast health.

Methods: This research used a qualitative approach to perform semistructured interviews with 11 high-risk women who had a family history of breast cancer recruited from the oncology department of a hospital using purposive and theoretical sampling during the period from August 2024 to April 2025. The analysis of the data was conducted using the grounded theory approach by Strauss and Corbin to formulate a theoretical model for breast self-examination practices.

Results: This study highlighted breast health education as a motivator of and the core category for breast self-examination practice. This study found perceptual, attitudinal, and familial support drivers of breast self-examination practice for early diagnosis of breast cancer and better living.

Conclusions: This study enhances the body of knowledge regarding the experiences of high-risk women. Health care providers play a significant role in using this framework to steer innovative educational interventions that promote breast health in culture-bound communities.

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KEYWORDS

breast self-examination practice; breast health education; breast cancer; high-risk women; breast self-examination

Introduction

Worldwide, 2.3 million women were diagnosed and 760,000 died of breast cancer (BC) in 2022 [1]. BC is the second most common type of cancer and among the major causes of pathological complications [2]. Approximately 15% to 20% of women diagnosed with BC have a family member who has also been diagnosed with the disease [3]. A family history of BC elevates the likelihood of developing the illness, particularly among close blood relatives who have had BC. Women with a first-degree relative (sister, daughter, or mother) diagnosed with BC face nearly double the risk. If a woman has 2 first-degree relatives diagnosed with BC, her risk increases by roughly 3 times [4].

In Asia, Pakistan records the highest rate of BC incidence at 23.1% [5]. Additionally, 23.8% of women in Pakistan have a family history of BC. The average age of family members diagnosed with BC has been found to be 49.2 years [6].

Moreover, 95.2% of these individuals have at least one family member who was affected. The most common relative diagnosed with BC is the mother, accounting for 47.6% [7]. The World Health Organization-recognized tools for BC screening are mammography, clinical breast examination, and breast self-examination (BSE) [1]. Although mammography has proven to be a reliable and valid BC screening method, awareness of this tool and its accessibility and affordability to women have been low in poor-resource countries [8]. BSE and clinical breast examination come in handy in such countries. BSE practice is a more acceptable method due to cultural issues, and evidence has proved that 40% of diagnosed BCs are detected through BSE [9], thus validating the usefulness of the procedure in BC screening [3].

Among high-risk Pakistani women with a family history of BC, merely 15% are knowledgeable about the disease, and only 4.18% use BSE as a screening measure for BC [10]. Just 1% regularly practices BSE, whereas 3.6% do so occasionally [11]. Furthermore, late-stage presentation of BC (stages III or IV) is

prevalent throughout the country, with nearly 35.2% of delayed cases occurring among high-risk Pakistani women [12]. It has been demonstrated that 40% of diagnosed BCs are identified through BSE [13].

In Pakistani culture, the concept of the “breast” is more associated with sexuality than with health, making discussions about it taboo due to conservative societal norms [14]. Cultural influences significantly affect breast health awareness among Pakistani women, with many refraining from performing BSE due to the stigma surrounding self-examination and embarrassment over discussing private body parts or undergoing medical assessment [15,16]. Misunderstandings, societal expectations, and false beliefs hinder the BSE practice and lead to delays in seeking help among women. The influence of culture has resulted in women not being motivated to carry out BSE or being taught how to [17].

Despite the significance of cultural values, there is a lack of research on the implementation of BSE practice measures among women at high risk. To improve this situation, it is essential to investigate the BSE practice viewpoints of high-risk women. This study used a grounded theory approach to create a conceptual understanding based on participants’ lived experiences, aiming to formulate a conceptual model or theory rooted in participants’ perspectives.

The purpose of this study was to explore and comprehend the experiences of high-risk women, focusing on their BSE practice and the factors that influence their effectiveness in managing breast health.

Methods

Study Design

This study used the grounded theory approach by Strauss and Corbin [18] and adhered to the COREQ (Consolidated Criteria

for Reporting Qualitative Research) checklist to ensure rigor [19]. Grounded theory is a qualitative research method aimed at developing a theory that is firmly based on data that are collected and analyzed systematically. This approach is especially effective for examining intricate social processes, such as BSE practice, as it seeks to understand how people develop and sustain behaviors about a specific health issue.

Participant Selection

The data were gathered between August 2024 and April 2025. The researchers applied both purposive and theoretical sampling to select data sources and participants. Oncology nurses asked 11 high-risk women to participate in the study, and no one declined to take part in the interviews. The timing and date were arranged based on the availability of the participants, and the researchers provided thorough explanations about the study. At first, purposive sampling was used to identify participants who met certain eligibility criteria: (1) female participants with mothers diagnosed with BC, (2) proficiency in the Urdu language, and (3) willingness to take part. When the investigation advanced, theoretical sampling was used to enhance evolving theory. Theoretical sampling is an iterative process in which data collection and analysis are conducted simultaneously, using the emerging analysis to guide the selection of subsequent data to collect. Collected data were coded and analyzed to form initial concepts, categories, and themes. The selection of new participants was based on their marital status (unmarried, married, or widowed) and level of education (primary school, middle school, tenth grade, or higher) to understand the concepts, fill the gaps, refine categories, and expand the theory. Theoretical sampling persisted until data saturation was reached, when no further relevant data or insights were produced. The aforementioned 11 high-risk participants from diverse communities took part in the study (Table 1).

Table 1. Participant characteristics.

Participant ID	Age (y)	Marital status	Educational level	Region
HRW1 ^a	21	Married	Tenth grade	Urban
HRW2	24	Married	Tenth grade	Urban
HRW3	22	Married	Primary school	Urban
HRW4	21	Unmarried	Tenth grade	Rural
HRW5	26	Married	Graduation (16 years of education)	Urban
HRW6	24	Married	Primary school	Rural
HRW7	22	Married	Primary school	Rural
HRW8	27	Married	Tenth grade	Urban
HRW9	24	Widowed	Primary school	Semiurban
HRW10	25	Married	Middle school	Rural
HRW11	23	Unmarried	Twelfth grade	Semiurban

^aHRW: high-risk women.

Ethical Considerations

The Research Ethics Committee of the Institute of Allied Health Sciences associated with the hospital provided ethics approval for this study, with reference IAHS/WMC/786/008-02. All participants provided informed consent, and information was provided on their right to leave the study at any point without facing repercussions. Participant data were anonymized to ensure confidentiality, and all research materials were securely stored. Participants were not provided any compensation for their participation.

Data Collection

Data were gathered through semistructured interviews (Table 2). These interviews were conducted in person, with audio

recordings made of participants, along with observations and verbatim transcriptions. Each interview lasted approximately 35 to 50 minutes. Field notes were kept providing contextual details. Several participants were interviewed more than once, with 81.8% (9/11) taking part in a second interview to enhance the data and facilitate clarification, deeper exploration, and a richer understanding of emerging themes. Data were gathered until data saturation was achieved, which is defined as the point at which no new themes or insights arise. Due to logistical constraints and participant preferences, transcripts were not returned to participants for member verification. Nonetheless, to maintain ethical standards and ensure the accuracy of the transcriptions, a method of double transcription and validation was used [20,21].

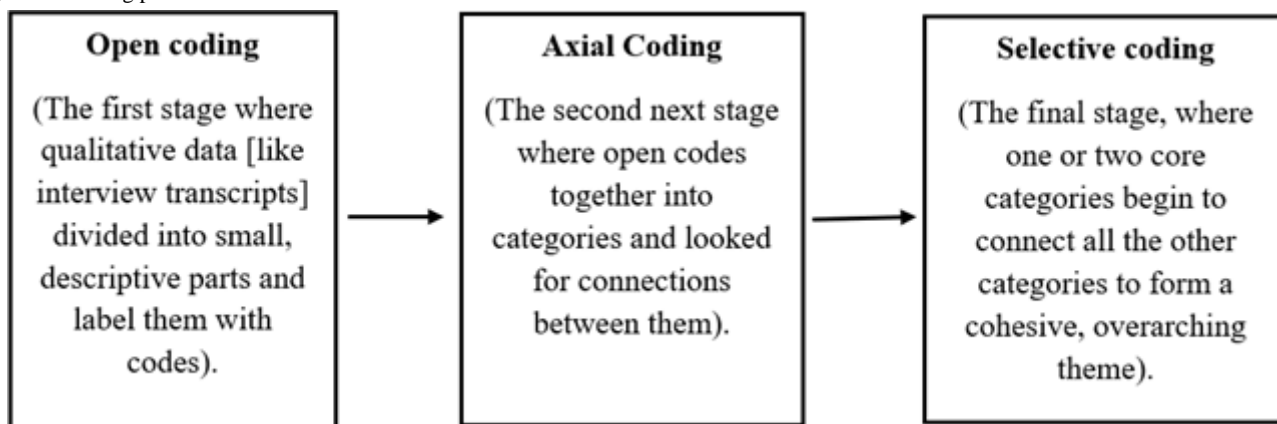
Table . Interview guideline.

Category	Questions
Opening questions	<ul style="list-style-type: none"> • “Do you think that you should take care of your breast health? Or do you think that breast health is important for women health?” • “What do you know about breast health as you are at risk of breast cancer or what do you know about breast cancer as your mother is suffering from the same condition?” • “Do you know how to do breast self-examinations practice or what are the methods of breast self-examination practice?” • “Do you examine your breast? Or do you think that you should do breast self-examination practice?”
Probing questions	<ul style="list-style-type: none"> • “Do you have the ability or confidence to do your breast self-examination practice?” • “What changes do you observe during breast examination?” • “Can you explain the change or discuss the changes with anyone, or do you think that change should be discussed?” • “What will you do to manage changes in your breasts to maintain your breast health?” • “Do you think that you need support or assistance, and how did you receive such support?”
Closing question	<ul style="list-style-type: none"> • “Is there anything you would like to share or add?”

Analysis

Analysis of the data was conducted following the grounded theory approach by Strauss and Corbin [18], which involved open, axial, and selective coding (Figure 1).

Figure 1. Coding process.



Coding of interview transcripts was done using verbatim data. Conceptual sensitivity to achieve reflexivity and analytic consensus was maintained by using multiple coders in discussion, where codes were reached through ongoing discussions and adjustments to the coding framework. The coding tree (Table 3) shows that the initial codes were organized into 5 subcategories under a single main category and were subsequently combined to create the final thematic model. Constant comparative analysis was used for the development

of themes, in which new data were continually assessed against existing codes and categories. This approach allowed for the refinement of the emerging theory and affirmed its applicability across diverse participant experiences [22,23], directed at identifying repeated patterns and connections within the data [20,24,25]. The process resulted in the documentation of the key themes: the desire for breast health awareness, family support, change in perceptions and attitude, and early diagnosis of BC (Figure 2).

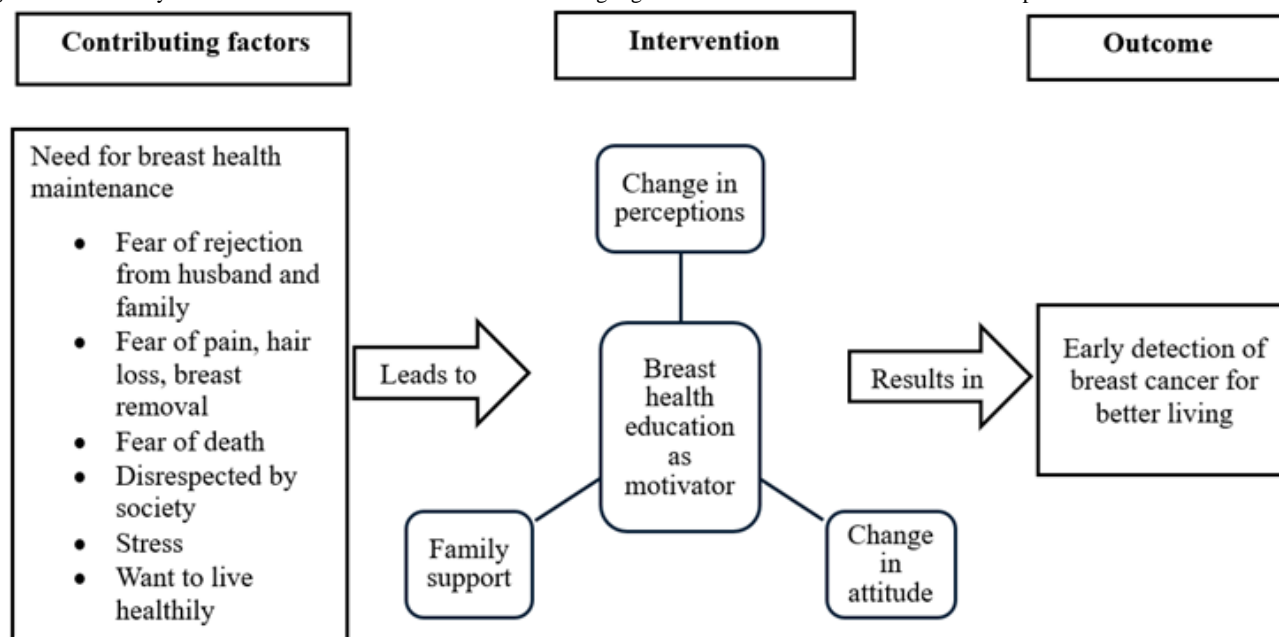
Table . Coding process for the category of breast health education as a motivator.

Level of coding	Code or category	Participant code
Open coding	<ul style="list-style-type: none"> • Realization of health issues related to BC^a. • Awareness of BC symptoms. Motivation to seek information about BC. • Cultural issues related to delay in health-seeking behavior. • Family support from mother • Change of perceptions • Breast health awareness • Change in attitude 	<ul style="list-style-type: none"> • “I know that I AM at risk of breast cancer because my mother is suffering from this and I saw my mother’s condition.” [Participant 1] • “My mother discusses her problems with me, and I feel her pain.” [Participant 5] • “My mother is suffering from pain, stress, hair loss, and many other problems.” [Participant 3] • “My mother told me that my condition was better if she know about breast cancer and she wish for me to have all information about breast cancer, and I also want to know about this.” [Participants HRW 5] • “My mother hides her problem from all family and when she can’t bear her problem than she disclosed to her mother-in-law and she agreed to visit the doctor.” [Participants HRW 7] • “I saw my mother’s condition, and I was worried. My mother guided me to touch the breast is not wrong it’s our body part; we can discuss our problems with lady doctor because she is also women like us. She can understand us.” [Participants HRW 4] • “I did breast examinations to feel any change in my breast like pain, swelling for early identification of cancer.” [Participants HRW 11]
Axial coding	<ul style="list-style-type: none"> • Category: BSE^b practice (subcategory 1: breast health maintenance; subcategory 2: symptoms awareness) • Category: influential factors (subcategory 1: change in perception of BC and BSE; subcategory 2: change in attitude; subcategory 3: family support) 	<ul style="list-style-type: none"> • Open codes: “I can do breast examination by touch and observation.” [Participant HRW 4] • Open code: “I know the symptoms like pain in breast, swelling in breast, discharge.” [Participant HRW 6] • Open code: “My mother told me that breasts are like other body parts, breast problems are like other problems of body, breast touch is not wrong.” [Participant HRW 9] • Open code: “Realizing the importance of early diagnosis, performing Breast examination.” [Participant HRW 11] • Open code: “I can understand breast health issues and have support from mothers in early health seeking behavior such as to visit doctor for my problem.” [Participant HRW 9]
Selective coding	<ul style="list-style-type: none"> • Category: breast health education as motivator 	<ul style="list-style-type: none"> • Realization of breast health issues, and need for BSE practice for identification of any breast change, and that leads to early BC diagnosis for healthy living

^aBC: breast cancer.

^bBSE: breast self-examination.

Figure 2. The theory of breast health education as a motivator among high-risk women for breast self-examination practice.



Credibility and Trustworthiness

The reliability and credibility of this study were maintained through implementation of several approaches as suggested by recognized qualitative research guidelines [26]. These included (1) member checking, in which initial interpretations and findings were shared with high-risk participants to check the accuracy and authenticity; (2) triangulation, which involved comparing various data sources—such as interview transcripts and field notes—to enhance the validity of the results; (3) investigator triangulation through ongoing team discussions during the data analysis phase to confirm consistency and individual bias reduction; and (4) an audit trail by keeping thorough documentation, such as coding decisions, to facilitate external review and transparency.

Results

The core category of the study was breast health education as a motivator, emphasizing the vital role that awareness and understanding of one’s breast health plays in promoting BSE practice for BC screening (Figure 2).

Contributing Conditions: Need for Breast Health Maintenance

Understanding the mother’s BC situation and being aware of BC symptoms such as pain or hair loss, fear of rejection from society, and stress creates the need for breast health maintenance and can inspire participants to take part in screening activities such as BSEs for early detection and instill hope for improved health. Family support, especially support from mothers who realized their own situation and understood their daughters’ need for breast health, motivated participants to change their perceptions of health care choices and the way in which they sought health services and build a positive attitude to engage in health-seeking behaviors such as BSE practice.

Intervention Conditions: Key Factors Influencing BSE Practice

Change in Perceptions

Cultural factors significantly influence health care choices and the way in which individuals seek health services. The participants recognized that being aware of breast health is a key aspect of women’s health. They adjusted their views regarding breast health and, through family support, appeared motivated to pursue health-seeking behaviors.

Change in Attitude

Cultural values shape women’s attitudes, leading to feelings of anxiety surrounding BC diagnoses and embarrassment when discussing the topic. Participants acknowledged the significance of early detection for improving quality of life and demonstrated motivation for maintaining breast health.

Family Support

In Pakistani culture, family support, particularly from mothers, plays an essential role in influencing their daughters’ perceptions regarding health care choices. The encouragement from mothers has a significant impact on promoting their daughters’ health.

Outcome: Early Detection of BC for Better Living

The objective of BSE practice is to facilitate the early identification of BC through health education, thereby enhancing quality of life and promoting better living. Early diagnosis of BC significantly increases the likelihood of survival for patients.

This core category emerged in various driving themes, such as the realization of breast health issues, the change in participants’ perceptions and attitude, and participants’ need for BSE practice for identification of any breast change that would lead to early BC diagnosis (Table 4).

Table . Major themes with participant quotes.

Theme	Participant quote
Need for breast health maintenance	<ul style="list-style-type: none"> “I am aware that I have a higher risk of developing breast cancer because my mother is currently facing this illness, and I have witnessed her suffering from pain, stress, hair loss, and various other challenges.” [Participant HRW 3]
Change in perceptions	<ul style="list-style-type: none"> “I observed my mother’s situation, and it concerned me. My mother taught me that examining our breasts is natural; it’s a part of our bodies, and we can talk about our issues with a female doctor because she is also a woman like us. She can realize our experiences.” [Participant HRW 4]
Change in attitude	<ul style="list-style-type: none"> “I possess knowledge about breast self-examination and various methods, like using my fingers to feel any changes in the breast, such as discomfort or swelling, and I can also monitor any change between both breasts.” [Participant HRW 11]
Family support	<ul style="list-style-type: none"> “My mother shares her issues with me; I empathize with her struggles. She mentioned that her situation could have improved if she had been informed about breast cancer, and she hopes I have all the knowledge regarding it, which I also wish to acquire.” [Participant HRW 5] “My mother reminds my sister and me to conduct monthly breast checks, always assuring us that she is by our side.” [Participant HRW 9]
Early detection of breast cancer for better living	<ul style="list-style-type: none"> “I perform breast examinations every month because I am aware of my mother’s situation; she was diagnosed very late. The doctors informed us that if she had been diagnosed sooner, her condition would be in a better state than it is now. Therefore, I have hope that I will not endure the same fate as my mother. I am determined to lead a healthier life.” [Participant HRW 1] “I perform breast self-examination regularly with a hope that I will live a healthy life.” [Participant HRW 8]

Discussion

Principal Findings

The results of this research highlight the importance of health education in encouraging BSE practice among Pakistani high-risk women. This research adds to the grounded theory concerning BSE practice by demonstrating how health education influences various elements of preventive and promotional health care, such as perceptual change, attitudinal change, and familial support for BSE. The primary theme, breast health education as a motivator, emerged as a key factor influencing behaviors related to BSE practice. This observation is consistent with the health belief model, which suggests that people are likely to engage in health-promoting behavior when they recognize a significant degree of susceptibility to a health issue [27]. The findings of this study on BC symptoms served as a trigger for embracing BSE practice, underpinning the idea that awareness of potential health risks fosters change in behavior [28].

This research emphasizes that educating individuals about breast health plays a critical role in encouraging them to perform BSE. Those with greater knowledge about BC were found to be more motivated to engage in practices that promote breast health. This highlights the significance of educational programs aimed at improving people’s understanding of BC, the misperceptions

about it and its associated risks, and the advantages of different screening strategies [29].

Knowledge affects an individual’s views and interpretations of sociocultural contexts, as well as their ability to foresee results and make choices. Greater awareness and a favorable change in perceptions of BC and the taboos of BSEs can greatly enhance BSE practice [30]. This aligns with the principles of social cognitive theory. According to social cognitive theory, knowledge affects perception by influencing how people decode social situations and anticipate outcomes [31].

Education about breast health can alleviate feelings of embarrassment and fear, resulting in a more favorable outlook on BSEs and the pursuit of medical consultations due to cultural impact [32]. These conclusions correspond with the change theory and the stages of change model by Lewin [33], which can be used to foster more constructive attitudes toward change. Individuals and groups adjust to new circumstances, handle resistance, and reinforce new behaviors [33].

Cultural context affects behavior change. The PEN-3 cultural model has also already demonstrated how cultural context matters in interventions, such as those for cancer awareness and screening [34]. Naturally occurring support from family members has been shown to increase healthy lifestyle behaviors such as BC screening measures (eg, BSE) through providing information and role-modeling. Family members have an impact

on women's decisions and actions throughout their BC journey, such as (1) confirming breast changes, (2) managing personal emotions, (3) seeking the information, (4) seeking alternative forms of treatment, and (5) advocating for conventional treatment [35]. Family support, especially from mothers, acts as a significant environmental factor that plays an important role in influencing BSE practice. Respectable family support increases a woman's awareness of and interest in undergoing early cancer screening. If a woman receives good emotional support, then she is more likely to behave well for her health [36].

The influence of culture on perception, attitude, and family support, especially from mothers, regarding BSE practice is a core observation of this study. The participants' ability to adopt cultural practices such as family support and change in perception of and attitude toward women's breast health in response to health needs determines the importance of culturally sensitive interventions [37]. This study highlighted the need for BSE practices that are culturally and contextually relevant, such as breast health education targeting participant negative cultural beliefs related to BC and BSE (eg, the taboo of touching oneself) by fostering positive perceptions of this body part, such as the fact that it is a woman's body part, which means that it is also a part of health and not only a part of sexuality, and fostering

a positive attitude about BC and its screening measures (eg, BSE) by encouraging women to talk about BC with their family members (eg, with their mothers). Family support motivates women regarding the fact that BSE is not a wrong concept. The breast is a part of their body, which they have a responsibility to be aware of. All these efforts will lead toward behavior change and the promotion of preventive behaviors.

Limitations

This study was carried out at a single hospital, representing a limited group of high-risk women in the area. Grounded theory seeks to create theories based on contexts and data, which might restrict the applicability of the results to different populations.

Conclusions

This study offers convincing evidence underscoring the vital role of breast health education in promoting BSE practices among high-risk women in Punjab, Pakistan. The findings provide essential insights into how improved breast health education can bring about positive changes in attitudes, perceptions, and the involvement of family support systems. This research marks the first effort to develop a grounded theory that presents a new conceptual model to understand the processes related to effective breast health management in similar culture-bound communities.

Funding

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Data Availability

The data from this study cannot be accessed publicly because of ethical reasons and the need to maintain the confidentiality of the participants.

Conflicts of Interest

None declared.

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Abbreviations

BC: breast cancer

BSE: breast self-examination

COREQ: Consolidated Criteria for Reporting Qualitative Research

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Effect of a Community-Based Enhancement Program on Emergency Assistance and Marine Patient Transfer Coordination Competency Among Community Health Volunteers on the Remote Islands of Southern Thailand: Quasi-Experimental Study

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Abstract

Background: Currently, remote areas face problems accessing health services. Although emergency medical systems have a policy of pushing more rapid response units into these communities, they still have not covered many areas due to the distance and the lack of a specific system that fits the community context. The resulting delays to medical treatment after accidents and emergency illnesses in these areas thus increase the risk of severe symptoms, disability, and subsequent death.

Objective: This study examines the effectiveness of a community-based enhancement program for emergency assistance and marine patient transfer coordination among community health volunteers (CHVs) on Phaluay Island, southern Thailand.

Methods: This quasi-experimental study followed a 1-group pretest or posttest design. The research sample consisted of 30 CHVs selected through nonrandom purposive sampling. The research instruments were demographic questionnaires, knowledge and skill measures of emergency assistance, and a competency assessment of marine patient transfer coordination. The data analysis employed descriptive statistics, repeated measures analysis of variance, and the Bonferroni test, with statistical significance set at P less than .05.

Results: The results revealed that the average scores on emergency assistance and marine patient transfer coordination knowledge were significantly higher ($P < .001$) after training compared to before, specifically at weeks 1 and 30. The average scores on emergency assistance and marine patient transfer coordination skills in weeks 1 and 30 in the CHVs were significantly higher ($P < .001$). The CHVs' mean scores for emergency assistance and marine patient transfer coordination competency before (at week 1) and after training (at week 30) were significantly higher ($P < .001$).

Conclusions: This research suggests that there is a need for policy advocacy by relevant agencies to further develop CHV competencies, which require continuous stimulation, monitoring, and reskilling to prepare these volunteers and other community members to respond effectively to emergencies in remote areas.

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KEYWORDS

knowledge; skill; training; technology; accident; health care; competency; marine transfer; remote Island; cardiopulmonary resuscitation; CPR

Introduction

The issue of health care system access remains a significant concern in various parts of the world [1]. As a middle-income country, Thailand needs to develop its structural and foundational systems to support its growing population, just as much as its aging citizens [2]. However, Thailand faces obstacles to structural development, such as inadequate transportation

[3]. This factor alone prevents various population groups from accessing medical care promptly, especially in remote and island areas [4]. Limited medical facilities that support potential treatment, as well as a shortage of health personnel who serve the people in these remote areas, pose further issues [5]. As in other Southeast Asian countries, there is a persistent shortage of medical personnel. Many countries in the region maintain a doctor-to-population ratio below the recommended standard of

10 per 10,000, especially in Cambodia, Indonesia, Laos, Myanmar, the Philippines, Thailand, Timor-Leste, and Vietnam. Cambodia reports the lowest ratio at 1.93 per 10,000, whereas Singapore achieves the highest ratio at 22.94 per 10,000 [6]. Although Thailand's emergency medical system has a policy of pushing more rapid response units into the community, it may not cover all areas [7]. The resulting delays in timely medical treatment after accidents and emergency illnesses increase the risk of severe symptoms, disability, and subsequent death [8].

Phaluay Island, an island located in Thailand's Surat Thani Province, has a population of approximately 500 people [9]. From the island, it takes more than 2 hours to reach the mainland by a small passenger boat. Emergencies such as motorcycle accidents and falls are common. As a result of its remoteness, Phaluay Island's population, including tourists who visit the site, has been deeply affected by these and other forms of accidents and emergency illnesses, though there are difficulties in mitigating this issue. According to local health officials, the island has 1 subdistrict hospital and only 2 public health personnel for health support. This limitation can affect life and health conditions during an emergency. Moreover, no referral system exists to facilitate effective care and assistance for patients on Phaluay Island.

To receive health care, the village residents have had to use expensive private boats or their own small longtail boats, the latter of which may be at risk during emergency transport due to wind and waves. Depending on wave conditions, transport to sufficient treatment facilities can endure for more than 2 hours. This may result in patients receiving insufficient care before arrival. Based on the data on illnesses and patient referrals from 2020 to 2022, 25 emergency cases from Phaluay Island required referral to a mainland hospital; of those, only a small percentage utilized emergency medical services. Most patients were transported via a small boat. These limitations put patients at risk of not receiving care from staff during transport.

This makes it essential to develop knowledge [10] and various competencies related to initial care during health emergencies on Phaluay Island [11]. In such situations, community health volunteers (CHVs) play a crucial role in supporting primary health care through adequate emergency response [12,13], as learned through sufficient knowledge and skill training [14]. Recent research has revealed the positive impact of scenario training on rural CHVs in emergency response situations [15]. There is also a less common training program that integrates digital technology specifically into the island context. In addition, guidelines for assistance and emergency referrals for people on remote islands in Thailand are being made available to the public [16]. One such development enables volunteer leaders to provide care and assistance in emergencies by integrating communication technology, including ambulance operation centers (AOCs), into the marine patient referral system.

This research, therefore, focuses on integrating Phaluay Island's AOC into its marine patient referral system to enhance patient care. This system has not yet been applied to small boat referrals, though utilizing technology can enhance this operational gap

[17] and meet Thailand's transformational needs [18]. This integration can serve as a guideline for strengthening and supporting individuals in remote areas to take care of themselves. It also involves coordinating with network partners to establish health care systems that enhance access to and promote equality in health care [19]. It may lead to the ultimate goal of people being safe, continuing to reduce the risk of disability and death rates.

Specifically, this study examines the effectiveness of a community-based enhancement program on emergency assistance and marine patient transfer coordination competency among CHVs on Phaluay Island, southern Thailand. We hypothesized that CHVs' competency in providing emergency assistance and coordinating marine patient transfers after receiving this training will be statistically significantly higher than before the training ($P < .05$). This paper also highlights the process and impact of integrating the community context, technology-based approaches, and situated learning theory in the program's development.

Methods

This research followed a quasi-experimental, 1-group pre- or posttest design. It represents the third phase of the research and development project "Enhancement of Assistant and Referral Systems for Accidents and Emergency Illness on a Remote Island: Phaluay Island Safety Model."

Research Sample

Study Participants

To determine the effectiveness of the primary care knowledge and competency development program, people living on Phaluay Island were recruited as CHVs via nonrandom purposive sampling. A total of 30 people were recruited based on the following criteria: 18 years of age or older, no physical or visual limitations, no congenital diseases such as heart disease or asthma, willing to participate in the entire research process, and the ability to read and write in Thai. All participants were recruited and contacted by local health personnel to participate in this research.

Sample Size Calculations

This research compared the volunteers' mean scores on knowledge and skills assessments. The researchers calculated the sample size based on a previous study that examined the effect of simulation training on enhancing nursing students' perceptions to engage patients' families in treatment plans [20]. With a power ($Z\beta$) of 80% (0.84), a significance level ($Z\alpha$) of 0.05 (1.96), a mean difference of 1.1 (SD1 0.6 and SD2 0.3), k of 1 group, and statistical significance of 0.05, the sample size obtained for this study was 22 cases. To counter the chance of participants dropping out of the research, the researchers increased the sample size to 30 according to Cohen formula ($n=22$ cases) [21]:

$$\text{Effect size} = d_{\text{pools}} = m_1 - m_2 = \frac{SD_1 + SD_2}{\sqrt{2}} = \frac{0.6 + 0.3}{\sqrt{2}} = 0.744$$

$$n = \frac{(Z\alpha/2 + Z\beta)^2 \times 2 \times \sigma^2 (1 - \rho) \delta^2}{\delta^2}$$

$$n = \frac{(1.96 + 0.84)^2 \times 2 \times (0.9)^2 (1 - 0.05) (0.744)^2}{0.744^2}$$

Research Instruments

Training and Data Collection

The research instruments consisted of 2 parts—the community-based enhancement program and the knowledge and skill measure of emergency assistance and marine patient transfer coordination competency. First, the community-based enhancement program utilized situated learning theory [22] as a framework for developing training activities. This theory focuses on learning as participation through social interaction and a community of practice in which the individual shares and learns together. The program activities are based on the elements of activities, artifacts, identities, and relationships.

These elements were intended to develop the sample group's knowledge and skills in providing basic health assistance to patients and referring marine patients. The details of the program are as follows: (1) organized activities, including lectures, demonstrations, reverse demonstrations, and practice

simulations, developed CHVs' diverse knowledge and skills; (2) artifacts involved the integration of AOC technology into potential development of the patient marine transfer support; (3) the program utilized 4 emergency simulation situations consistent with the Phaluay Island community's identity and way of life to promote the application of available resources; and (4) emphasis on relationships promoted learning together in a group. The training program covered 5 operational stations: station 1, covering symptom assessment and first aid; station 2, on resuscitation and automated external defibrillator (AED) use; station 3, introducing maritime rescue and referral methods; station 4, concerning requests for assistance and communication; and station 5, for the implications of AOC system technology (Table 1). The development of these 5 station activities was underpinned by the elements of situated learning theory, which enhanced competency, knowledge, and skills in initial assistance for emergency patients, as well as the referral of marine patients from remote islands.

Table . The 5-station training program based on situated learning principles.

Station	Learning objectives	Duration (min)	Learning methods	Expected competencies
1. Symptom assessment and first aid	<ol style="list-style-type: none"> 1. Conduct rapid assessments of emergency symptoms using a structured methodology. 2. Identify clinical red flags and determine criteria for urgent referral. 3. Provide immediate first-aid interventions appropriate for common emergencies encountered in the island context. 	50	Instructional strategies included realistic scenario briefings, guided practice with authentic cases, peer coaching, facilitator feedback, and integration of local contextual cues.	Expected outcomes are accurate primary assessments, effective prioritization, safe first-aid interventions, and timely escalation decisions.
2. Resuscitation and AED ^a use	<ol style="list-style-type: none"> 1. Demonstrate high-quality cardiopulmonary resuscitation in accordance with American Heart Association guidelines. 2. Operate an AED correctly, including accurate pad placement, completion of safety checks, and appropriate shock delivery. 3. Coordinate team roles effectively during resuscitation, functioning as either a team member or leader. 	60	Practice skills through simulation activities, team-based scenarios with defined roles, ongoing coaching, and structured debriefing sessions that focus on decision-making within time and distance limitations.	Competencies include proper execution of cardiopulmonary resuscitation steps, effective chest compressions, safe and accurate use of an AED, clear team communication, and rapid response.
3. Maritime rescue and referral procedures	<ol style="list-style-type: none"> 1. Demonstrate safe maritime rescue principles and effective patient stabilization techniques for sea transfer. 2. Prepare patients for referral, including appropriate positioning, monitoring, and securing. 3. Utilize a standardized referral pathway for patient transfer from remote islands, specifying contact persons, timing, and required information. 	60	Contextual demonstrations of boat and shore transfer workflows, task-based learning activities, and hands-on equipment handling.	Competencies include safe patient handling and movement, implementation of stabilization steps, risk mitigation for weather and sea conditions, accurate referral preparation, and completion of performance checklists with scenario-based decision points.
4. Requesting assistance and emergency communication	<ol style="list-style-type: none"> 1. Demonstrate effective communication with dispatch and health services. 2. Deliver complete and accurate information to support decision-making processes. 	50	Role-play exercises involving caller, dispatcher, and team roles; both scripted and unscripted communication drills; structured feedback on clarity and completeness; guided reflection on authentic community communication barriers.	Demonstrate clarity, completeness, and timeliness in communication; route requests appropriately; confirm and close communication loops; and achieve proficiency as measured by a communication rubric and call simulation.

Station	Learning objectives	Duration (min)	Learning methods	Expected competencies
5. Implementation of technology and the AOC ^b system for marine transfer	<ol style="list-style-type: none"> 1. Demonstrate understanding of AOC functions, including coordination, dispatch, tracking, and documentation. 2. Apply AOC-supported workflows, such as request initiation, status updates, and referral coordination. 	50	System walk-through, hands-on practice with demonstration interfaces and workflows, case-based discussions on changes introduced by AOC, troubleshooting exercises, and reflective debrief sessions.	Competencies include accurate data entry and reporting, adherence to the correct workflow steps, timely updates and escalations, handling connectivity limitations, and successful completion of a task checklist.

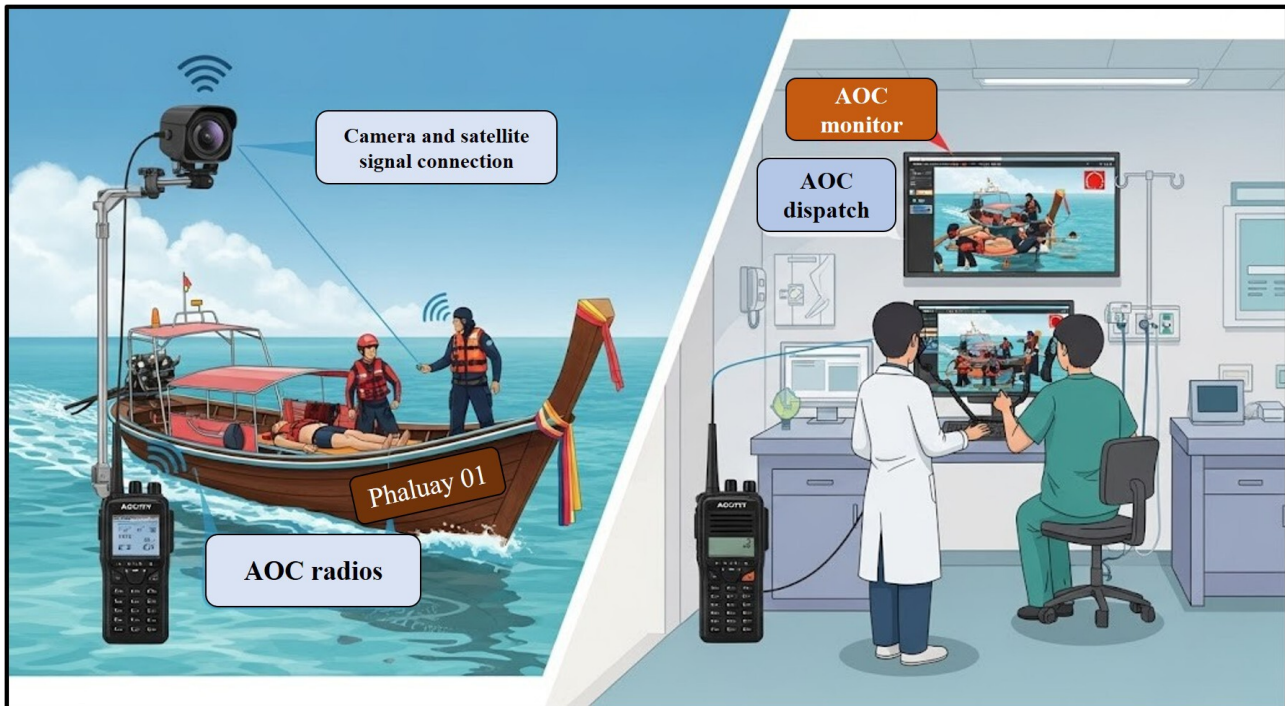
^aAED: automated external defibrillator.

^bAOC: ambulance operation center.

The program was conducted in 2 phases (30 weeks apart) for a total activity period of 12 hours. The training program included two components: (1) knowledge enhancement regarding first aid, basic life support (BLS), AED use, AOC, and communication in emergencies, and (2) skill development, consisting of demonstrating and then returning to demonstrate first aid, BLS, AED use [15,23], AOC implementation, communication activities, and maritime transfer. Activities of this phase fell into one of the following categories:

- Activities focusing on knowledge development over two and a half lecture hours to educate on fundamental assistance issues, such as symptom assessment, requesting help (emergency call number 1669), and communicating with the emergency medical system
- Workshop activities (1 h) on basic communication and assistance tools connecting to the AOC system
- Activities to develop competency in initial assistance and maritime referrals, such as condition assessment, movement, communication, and symptom monitoring, with the sample divided into groups in initial assistance exercises of 4 hours and 30 minutes each
- Activities to restore knowledge and skills in simulations (4 h each) in week 30
- An AOC equipment setup activity, as supported by TELY 360, demonstrated how to integrate the equipment into marine patient referral systems. This satellite signal connection device is used to track coordinates and locations during patient transfers, a common practice in secondary and tertiary health service facilities in Thailand. In the context of remote islands, the AOC was the first contact that the island had with the mainland. In addition, AOC devices, including radios to coordinate patient details with the operation center at Donsak Hospital and camera equipment to monitor patient status and referral teams (eg, CHVs and family caregivers), can be installed on the subject when a ready-to-use referral is available. This technological integration is a crucial component that enables the destination hospital to guide the referral team on board the ship during patient transport. The AOC device was placed in a portable box (as shown in Figure 1), and a designated, ready-to-use storage point was established for emergency patient transport in key areas, as agreed upon by the community.

Figure 1. Ambulance operation center (AOC), generated using Google Gemini (artificial intelligence image generator), 2025 [24].



The second part of the research instruments used for data collection were demographic characteristic questionnaires, the questionnaire of knowledge measurement, and the questionnaire of skill measurement, which are described as follows.

Demographic characteristic questionnaires gathered data on the volunteers' age, occupation, and education level; number of experiences providing basic health care assistance to victims of accidents or emergency illnesses; experience in helping with marine patient transport; and BLS experience.

The researchers developed a multiple-choice knowledge measure of emergency assistance and marine patient transfer coordination competency among the CHVs based on a literature review of relevant research. Each question had 2 answer options ("yes" or "no"), with 1 point given for a correct answer and 0 points for a wrong answer. There were 15 questions, leading to possible total scores of 0 to 15 points. This questionnaire involved evaluating the situation, emergency notification, and first aid for patients who met with an accident in situations such as poisonous animal bites, hemostasis, basic immobilization, and BLS.

The researchers also derived a skill measure of emergency assistance and marine patient transfer coordination competency among CHVs based on a literature review. The measurement had a 3-level rating scale. The program instructors performed a skill assessment during practice activities by selecting 1 answer that matched each participant's practice status: a complete practice yielded 2 points, an incomplete practice 1 point, and nonpractice 0 points. Participants could receive a total score between 0 and 36 on this 18-item questionnaire. This skill

measurement focused on symptom assessment, communication, first aid, and BLS.

To evaluate assistance competency and marine patient transfer coordination, the researchers further assessed the volunteers' total knowledge and practical skills scores, with scores ranging from 0 to 51 points.

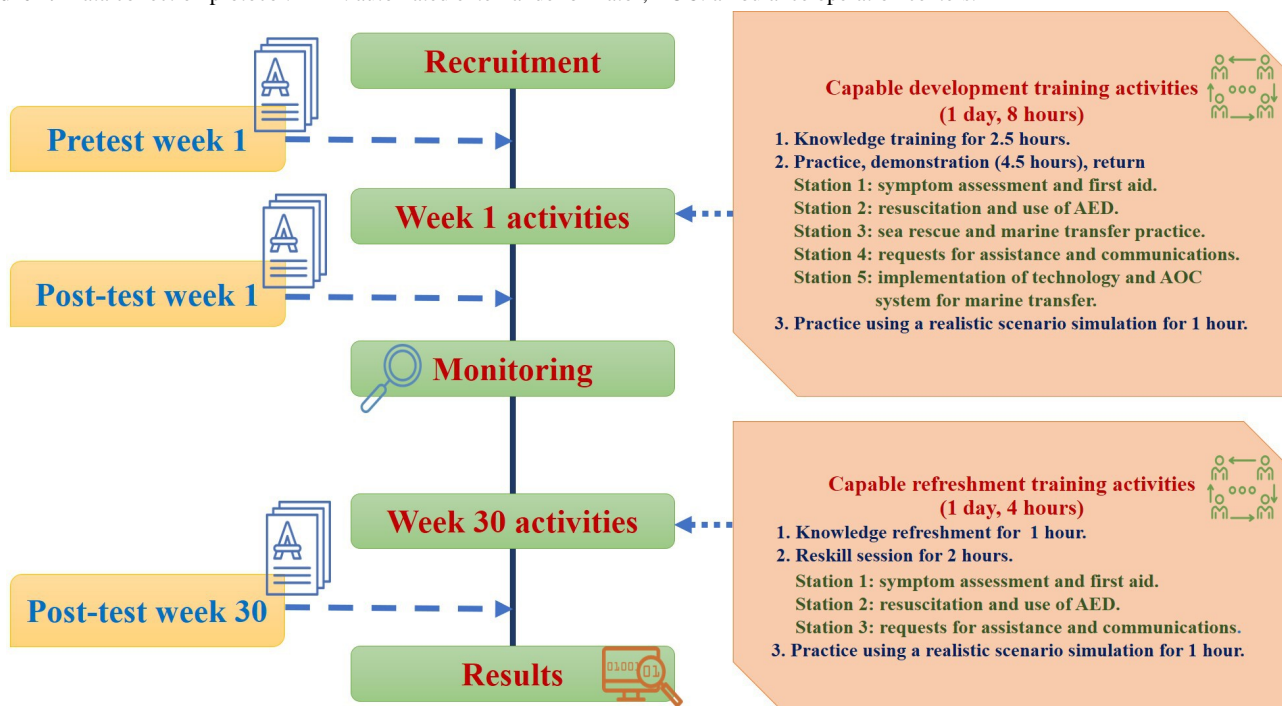
Instrument Validity

Five qualified experts examined the research instruments to determine whether their content validity ratio values exceeded 0.99, except for the following exceptions: item 7 of the demographics instrument, item 2 of the knowledge measure, and items 4 and 8 of the skill measure. The experts provided improvements, and the researchers implemented them accordingly. Considering the questionnaires' content validity index (CVI) results, the knowledge measure had a CVI of 0.98, and the skill measure had a CVI of 0.97. The researchers then administered each questionnaire to a pilot group of 30 people with characteristics similar to the sample. The reliability of the knowledge measure was also examined using the Kuder Richardson 20, which yielded a value of 0.737, while the skill measure yielded a Cronbach α coefficient of 0.964.

Data Collection

This research, in particular, was conducted between March and October 2024. After receiving ethics committee approval, the researcher proceeded to recruit the sample group to participate in the research process for a total of 30 weeks. The sequence of the quasi-experimental research process is outlined in [Figure 2](#).

Figure 2. Data collection protocol. AED: automated external defibrillator; AOC: ambulance operation centers.



Data Analysis

The demographic data were analyzed using descriptive statistics such as frequency, mean, percentage, and SD. The inferential statistics repeated measures ANOVA and the Bonferroni test were used to compare the mean differences in emergency assistance and marine patient transfer coordination knowledge, skills, and competencies among the volunteers before and after training at week 1 and week 30, respectively, with statistical significance set at $P=.05$.

Ethical Considerations

This project was approved by the Human Research Ethics Committee of the Surat Thani Provincial Health Office (approval STPHO2023-318). The researchers followed the principles of the Belmont Report to ensure the protection of the volunteers regarding respect for persons, beneficence, and justice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) [25]. The volunteers received sufficient information before deciding to participate in the project and signing the consent form. The participants could withdraw from the project at any time without penalty or

adverse effect. The participants’ information, including names and initials, was anonymized. All results will be presented and published for academic purposes and will be deidentified. The data and materials relevant to the participants will be stored in a secure room and destroyed 5 years after the first day of data collection. The participants in this study received a cash payment of 100 Thai baht per person for their time. They were also provided with one lunch (120 Thai baht; an exchange rate of US \$1=32.6 Thai baht is applicable) and two snack breaks (30 Thai baht each). The total value provided was 280 Thai baht per participant.

Results

From the preliminary analysis of the 30 CHVs, the sample group’s information was complete, and the data from 25 cases were analyzed because of 5 participants withdrawing from the project for personal reasons. The results showed that the sample had an average age of 48.20 (SD 13.43) years, and most individuals worked as freelancers. Forty percent (10/25) were involved in CHV work, while the majority had no experience in emergency aid (17/25, 68%), as shown in Table 2.

Table . Volunteer demographic data and emergency assistance experience (N=25).

Demographic data	Values
Career, n (%)	
Government officer	1 (4)
Farmer	3 (12)
Fisherman	1 (4)
Freelancer	10 (40)
State enterprises	2 (8)
Own business	8 (32)
Education level, n (%)	
Grade 6	15 (60)
Junior high school	4 (16)
Senior high school	3 (12)
Undergraduate	3 (12)
Role in the community, n (%)	
Community health volunteer	10 (40)
Community leader	2 (8)
Security officer	1 (4)
No specific role	12 (48)
Experience with emergency assistance, n (%)	
No	17 (68)
Yes	8 (32)
Age (y), range; mean (SD)	20-69; 48.20 (13.43)
Frequency of emergency assistance experience, range; mean (SD)	0-10; 1.52 (3.22)
Frequency of the marine patient transfer experience, range; mean (SD)	0-10; 1.53 (3.17)
Frequency of emergency calls experienced, range; mean (SD)	0-10; 0.64 (2.07)

A repeated measures ANOVA (n=25) revealed significant within-subject effects for all knowledge, skill, and competency. Knowledge scores increased significantly over time, $F_{(1, 24)}=41.379, P<.001$, with a large effect size ($\eta^2p=.633$; estimated mean, 95% CI 8.782 - 10.312). Skill scores change significantly,

$F_{(1, 24)}=58.532, P<.001$, with a large effect size ($\eta^2p=.709$; estimated mean 95% CI 23.815 - 25.012). Competency scores also demonstrated significant improvement, $F_{(1, 24)}=37.755, P<.001$, with a large effect ($\eta^2p=.611$; estimated mean 95% CI 32.817 - 35.103), as shown in Table 3.

Table . The variance of the variable within the training group for knowledge, skill, and competency (N=25).

Variable	SS ^a	MS ^b	F test (df)	P value	$\eta^2 p^c$	95% CI
Knowledge (error)	66.667 (38.667)	66.667 (1.611)	41.379 (1, 24)	<.001 ^d	0.633	8.782-10.312
Skill (error)	499.280 (204.720)	499.280 (8.530)	58.532 (1, 24)	<.001 ^d	0.709	23.815-25.012
Competency (error)	126.960 (257.880)	126.960 (10.745)	37.755 (1, 24)	<.001 ^d	0.611	32.817-35.103

^aSS: type III sum of squares.

^bMS: mean square.

^c η^2 : partial eta squared (effect size).

^dSignificant at $P<.001$.

The average scores on emergency assistance and marine patient transfer coordination knowledge before and after training, specifically at weeks 1 and 30, revealed that the CHVs' level of knowledge was significantly higher ($P<.001$). When

comparing pairs using the Bonferroni method, the average knowledge score before week 1 and before the formal start of the knowledge training likewise showed a statistically significant increase ($P<.001$). Between week 30 (after the program took

place) and before the knowledge training began, there was also a statistically significant increase ($P<.001$). However, following

the trials in week 1 and week 30, there were no statistically significant differences ($P=.39$), as shown in [Table 4](#).

Table . Average scores on emergency assistance and marine patient transfer coordination knowledge before and after training (N=25).

Time	Score, mean (SD)	Before training	Week 1, MD ^a (<i>P</i> value ^b)	Week 30, MD (<i>P</i> value ^b)	<i>P</i> value ^c
Before training	7.36 (2.039)	— ^d	3.52 (<.001)	3.04 (<.001)	<.001
Week 1	10.88 (2.369)	—	—	-0.48 (.39)	—
Week 30	10.40 (2.432)	—	—	—	—

^aMD: mean differences (time 2 – time 1).

^bBonferroni test for pairwise comparisons.

^cRepeated measures ANOVA for test of within-subject effects.

^dNot applicable.

The average scores on emergency assistance and marine patient transfer coordination skills in weeks 1 and 30 in the CHVs were significantly higher ($P<.001$). When comparing pairs using the Bonferroni test in week 1 and before the training, the mean skill scores were statistically significantly different ($P<.001$). In

week 30 and before the training, there was also a statistically significant difference in the skill level ($P<.001$). After the trials in weeks 1 and 30, the CHVs' average skill levels were significantly different ($P=.005$), as shown in [Table 5](#).

Table . Average scores on emergency assistance and marine patient transfer coordination skills before and after training (N=25).

Time	Score, mean (SD)	Before training	Week 1, MD ^a (<i>P</i> value ^b)	Week 30, MD (<i>P</i> value ^b)	<i>P</i> value ^c
Before training	21.00 (1.871)	— ^d	3.92 (<.001)	6.32 (<.001)	<.001
Week 1	24.92 (1.631)	—	—	2.4 (.005)	—
Week 30	27.32 (3.579)	—	—	—	—

^aMD: mean differences (time 2 – time 1).

^bBonferroni for pairwise comparisons.

^cRepeated measures ANOVA for test of within-subjects effects.

^dNot available.

The average scores on the CHVs' overall emergency assistance and marine patient transfer coordination competencies before and after training, specifically in weeks 1 and 30, showed a significantly higher competency mean score among the CHVs ($P<.001$). Upon pair comparison using the Bonferroni test, the competency mean scores at week 1 and before training showed

a statistically significant difference ($P<.001$). After the experiment at week 30 and before training, the competency levels were statistically significantly different ($P<.001$). Weeks 1 and 30 were also statistically significantly different ($P=.006$), as shown in [Table 6](#).

Table . Average scores on overall emergency assistance and marine patient transfer coordination competencies before and after training (N=25).

Time	Score, mean (SD)	Before training	Week 1, MD ^a (<i>P</i> value ^b)	Week 30, MD (<i>P</i> value ^b)	<i>P</i> value ^c
Before training	28.36 (0.568)	— ^d	7.44 (<.001)	9.36 (<.001)	<.001
Week 1	35.80 (0.590)	—	—	1.92 (.006)	—
Week 30	37.72 (0.908)	—	—	—	—

^aMD: mean differences (time 2 – time 1).

^bBonferroni for pairwise comparisons.

^cRepeated measures ANOVA for test of within-subjects effects.

^dNot available.

Discussion

Principal Results

In accordance with the research hypothesis, the CHVs' competency in providing emergency assistance and coordinating marine patient transfers after receiving this training will be statistically significantly higher than before the training ($P < .05$). The critical results indicate that there was a significant increase in the level of knowledge, skills, and competency in emergency assistance and marine patient transfer coordination from the first week after training to the 30th week.

Strengths and Limitations

This research's key strength is its integration of a new technology, AOC, into the training of CHVs. It also provides realistic scenarios based on community contexts gathered from community member recommendations. However, it may be limited by a lack of confidence in using the technology, which is new and exciting, among volunteers. This factor might inhibit this technology's full potential from being realized. Therefore, CHVs' technology competencies need to be developed regularly and continuously trained to eliminate their unconfident practice to prepare for the situations faced by people in the community. An additional constraint of this study was that participants were recruited via purposive sampling, which may limit external validity and introduce selection bias. Therefore, future studies should consider random, stratified, or cluster-based sampling for participant recruitment. Another limitation in this research needs to be addressed, specifically the gap between week 1 and week 30, during which no boosting activity was conducted, and it may affect their knowledge stability. Consequently, a further training program should consider incorporating booster activities via online sessions to monitor their knowledge and confidence in emergency illness assistance.

Comparison With Previous Work

The findings of this study are similar to previous research, which suggested that continuous training in BLS and first-aid skills helps trainees maintain better skills and competencies in the long term [26,27]. The results of this study reflect the effectiveness of the proposed training program in CHVs' continuous development, both in decision-making and practical skills, as well as their overall understanding of patient referral. This finding is consistent with a recent study by Pongtriang et al [15,23], who emphasized the importance of organizing continuous training programs and conducting long-term monitoring to encourage trainees to learn skills in-depth and maintain them for a longer period [28]. Indeed, competency levels can decrease significantly over time [29]. This result indicates that CHVs still require review and periodic knowledge updates [30] to be able to provide emergency assistance and transfer marine patients effectively. Another recent study highlighted that regularly restoring knowledge and skills helps slow down the rapid decline in competency levels that can occur after an initial training session [31]. Therefore, the findings of this study, where rehabilitation activities were held in week 30, effectively support long-term competency maintenance.

However, the study also revealed that the level of emergency assistance knowledge and skills among the CHVs was low overall. It is therefore important to raise awareness among nurses and other health officials of the need to study the context and background factors of people in their area to develop their potential [32], such as through the strategies tailored to this study. The recent study also suggests that considering the community context is an essential component in successful health development [33]. When analyzing the sample's background, it also became evident that the volunteers' education level was relatively low. Most participants had no experience assisting or responding to accidents and emergency illnesses. These factors contribute to insufficient knowledge and inadequate practices relevant to emergency assistance [34], making it crucial to maintain CHVs' knowledge and skills. This could be improved through government support for regular training on BLS and similar emergency issues [35].

Although Thai government legislation mandates that development initiatives take place at least once per year [36], inequity and insufficient development persist due to Phaluy Island's isolated location. This research finding aligns with a previous study, which identified several barriers to providing quality health care in rural communities [37] that require advanced care strategies, such as telehealth and satellite care, to close the health care gaps [38]. Our research incorporated digital technologies into a training program to continuously enhance the capabilities of the island's community members. This development can be considered a new approach to promoting prehospital care through technological support systems [39]. An improved referral system can also be achieved by enhancing the abilities of community volunteers to support their community's emergency care system. Using digital technology can aid communication, monitoring patient status [40], and facilitating the work of CHVs and family caregivers while transporting patients as well. Furthermore, the recent study supports that technology would be an advantage for community training in improving the competency of health care volunteers in the community [41]. Indonesia and the Philippines, similar to other Southeast Asian countries, encounter substantial challenges in marine health management, which necessitate the adoption of solutions, such as telemedicine systems [42]. In addition to technological interventions, the development of integrated national policies, including explicit legislation and dedicated funding for air and sea medical referrals, can address coordination barriers and reduce related costs [43]. Furthermore, strengthening community knowledge and attitudes through partnerships with local leaders may reduce delays in family decision-making and enhance understanding of health insurance systems [44].

Although previous studies have found the advantages of integrating technology to enhance people's potential holistically, our study found that unfamiliar technologies are challenging for volunteers, resulting in excitement and anxiety about using the equipment, which affects confidence in practice. These insights were drawn from the low level of practice scores in the first trial. In addition, the issue of communicating emergency medical incidents to the emergency dispatch staff revealed that a majority of participants in the sample group were not confident

and were anxious about communicating important and necessary information relevant to an incident [45]. Therefore, training with a clear format to practice both the use of necessary technologies and effective communication [46], using a step-by-step framework that can be followed and practiced independently [47], will be an important part of building confidence in developing first-aid skills and communicating more effectively in emergency confrontations [48]. When considering the knowledge and skills development program of this research, which utilized the concept of situated learning theory [22] as a framework for organizing activities to develop volunteers, the theory focuses on learning in collaborative learning situations through team participation. It is considered a highlight that is consistent with the situation and learning the context [49] of the group to understand its limitations, including support and resources for assistance at the scene, leading to problem solving and helping patients and injured people with the realistic context and situation [50], such as applying natural tools or materials in the vicinity to immobilize and move, among others. Addressing this situation is particularly important for areas with limited access and insufficient health support [51]. The findings of this development are important for the further development of training programs to enhance the knowledge and skills of volunteers in the area, which are tailored to the local context and leverage technology connectivity. This encouragement enables tracking and support for people and caregivers during the transfer, ensuring the safest possible outcome.

Implications for Practice

Health care providers play a crucial role in establishing community training, which necessitates consideration of community context through community engagement, such as the limitations of a local health care system, the level of digital literacy of community residents, the level of social participation, and the issue of community needs of competencies development to effectively enhance the abilities of CHVs and develop an appropriate training program to maintain their knowledge and

skills. In addition, due to its remote island location, similar to our study site around the world, there are several limitations to health care, support, and access to resources. With these limitations, community nurses and health providers could play an advocacy role by supporting the local people's need for emergency care system support with community health data and presenting to higher government agencies to encourage more attention to establish a policy-driven approach to health care accessibility [52]. In addition, the result of this study could be scaled up via provincial health offices to strengthen island-based emergency medical services in southern Thailand.

Conclusions

This study presented comparative findings on the competence, knowledge, and skills of local CHVs in providing first aid for emergency illnesses, accidents, and marine transfers of patients in a remote island area. This training program was developed based on the context, limitations, and stakeholder needs of Phaluay Island in southern Thailand. The training program utilized various methods that CHVs employ to prevent illness and attend to emergencies among the public. The findings revealed that the competence development program, which integrated digital technology to communicate with hospitals and monitor patients during rescue and transport to the destination hospital, can improve the CHVs' knowledge and skills in terms of assessing patient condition, requesting help in an emergency, communicating effectively, BLS, and AED use. The training can also assist with coordination and practices during patient transport for effective initial care. The results further demonstrated that the application of situated learning theory, the community context, and technology integration, with appropriate components, can improve the CHVs' competence and learning outcomes. However, to support the continuity and sustainability of competence in the long term, it is necessary to study development strategies that follow the changing context and relevant community factors. This may improve access to emergency medical services for local people and reduce the likelihood of disability and subsequent mortality.

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Data Availability

The datasets in this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AED: automated external defibrillator
AOC: ambulance operation center
BLS: basic life support
CHV: community health volunteer
CVI: content validity index

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Cumulative High-Risk Pregnancy Complications and Stunting Risk in Indonesian Children Younger Than 5 Years: Retrospective Analysis Using the Developmental Origins of Health and Disease Framework

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Abstract

Background: Stunting affects 21.6% of Indonesian children younger than 5 years, with complications from high-risk pregnancies (HRPs) identified as a potential risk factor. The Developmental Origins of Health and Disease framework suggests that prenatal exposures may permanently alter physiological development and disease susceptibility later in life.

Objective: This study aimed to examine the cumulative effects of HRP complications on the risk of stunting in Indonesian children younger than 5 years while controlling for socioeconomic confounders.

Methods: A retrospective study was conducted in Sleman Regency, Indonesia, analyzing 450 children (300 children with stunting and 150 children without stunting) aged 12 to 59 months. Data were collected from maternal medical records, maternal and child health handbooks, and integrated health post reports. Multivariate logistic regression was used to adjust for socioeconomic confounders including maternal education, family income, and antenatal care (ANC) visits.

Results: Mothers of children with stunting had significantly higher rates of any HRP complications (206/300, 68.7% vs 48/150, 32%; $P < .001$). After adjustment, multiple HRP complications (≥ 2 conditions) showed the strongest association with stunting (adjusted odds ratio [aOR] 5.80, 95% CI 3.26 - 10.32), exceeding the risk associated with individual complications such as anemia (aOR 3.21, 95% CI 2.12 - 4.86) or preeclampsia (aOR 4.37, 95% CI 2.18 - 8.76). Maternal education (aOR 0.72, 95% CI 0.58 - 0.89), family income (aOR 0.68, 95% CI 0.52 - 0.89), and ANC visits (aOR 0.85, 95% CI 0.76 - 0.95) were identified as protective factors.

Conclusions: The dose-response relationship between cumulative HRP complications and stunting supports the Developmental Origins of Health and Disease hypothesis. Current ANC protocols emphasizing single risk factors may be insufficient. Integrated prenatal care addressing cumulative risks is essential for stunting prevention in Indonesia.

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KEYWORDS

pregnancy complications; maternal health; high-risk pregnancy; child nutrition disorders; stunting; Developmental Origins of Health and Disease

Introduction

Overview

Stunting, defined as height-for-age z score ≤ -2 SDs below the World Health Organization (WHO) Child Growth Standards median [1], represents a chronic nutritional disorder reflecting failures in health, nutrition, and psychosocial care [2]. Globally, an estimated 149 million children younger than 5 years were

stunted in 2023, with the burden disproportionately concentrated in low- and middle-income countries (LMICs) [3]. Indonesia reports one of Southeast Asia's highest stunting prevalence rates at 21.6% according to the 2023 National Nutritional Status Survey [4], though this masks significant regional disparities ranging from 7.2% in Bali to 39.4% in Central Papua [5]. Beyond short stature, stunting leads to irreversible cognitive deficits [6], reduced educational attainment, lower adult productivity, and intergenerational poverty perpetuation [7].

This original research article aims to examine the cumulative effects of high-risk pregnancy (HRP) complications on the risk of stunting in Indonesian children younger than 5 years, applying the Developmental Origins of Health and Disease (DOHaD) framework.

The DOHaD hypothesis provides a critical framework for understanding stunting etiology. First, proposed by Barker (1990) and later expanded by Hanson and Gluckman (2015), this theory posits that environmental exposures during sensitive developmental windows have permanent effects. Recent reviews have increasingly emphasized that these effects are often the result of cumulative and synergistic exposures, rather than single insults [8], which forms the central hypothesis of our study. These exposures can alter physiological structure, metabolic programming, and disease susceptibility later in life [9,10]. Central to this concept is fetal programming, where prenatal insults such as those from HRP complications disrupt normal development [11]. In LMICs like Indonesia, where 48.9% of pregnant women experience anemia [12], the interplay between maternal nutritional status, HRP complications, and child growth outcomes represents a critical pathway [13].

HRP complications, including anemia, preeclampsia, gestational diabetes mellitus (GDM), heart disease, and asthma, expose fetuses to nutrient deprivation, hypoxia, oxidative stress, and inflammation [14]. Maternal nutrition plays a critical role in fetal development, with deficiencies in key nutrients including iron, folate, and protein contributing to both HRP complications and subsequent child stunting [15]. Recent evidence suggests these effects may be cumulative, with multiple HRP complications synergistically increasing stunting risk beyond individual conditions [16-18]. For instance, a mother with both anemia and preeclampsia may expose the fetus to combined insults that disrupt fetal programming more severely than either condition alone [19]. However, most research examines HRP complications in isolation, with limited studies assessing their combined effects on stunting in Indonesia [20].

Despite Indonesia's National Stunting Acceleration Strategy (2023 - 2024), which emphasizes integrated nutrition interventions and antenatal care (ANC) strengthening, stunting prevalence remains above the WHO's significance threshold (>20%) [21]. Current ANC protocols primarily focus on identifying single risks such as anemia or preeclampsia [22], potentially overlooking pregnancies with overlapping complications that confer exponentially higher risk [23]. Furthermore, the role of socioeconomic confounders such as maternal education, family income, and health care access requires careful consideration to clarify the independent association between HRP and stunting [24].

This study addresses these gaps by doing the following:

1. Analyzing the comprehensive association between HRP history and stunting in Indonesian children younger than 5 years using contemporary international guidelines [22,25]
2. Controlling for key socioeconomic and health care-related confounders
3. Applying the DOHaD framework to interpret findings within Indonesia's public health context

4. Providing evidence for integrated prenatal care approaches that address cumulative risks rather than isolated complications.

Key Messages

The key messages for this study are as follows:

1. Cumulative maternal complications during pregnancy significantly increase the risk of stunting among children younger than 5 years.
2. Integrating maternal health monitoring into early child nutrition programs may help prevent intergenerational undernutrition.
3. Findings support the DOHaD framework, emphasizing the importance of prenatal care quality for child growth.
4. Strengthening ANC screening for HRPs could be an effective policy to reduce stunting prevalence in Indonesia.

Methods

Study Design

A retrospective analytical study was conducted in Sleman Regency, Yogyakarta Special Region, Indonesia, between January 2019 and December 2024. The design followed the life course epidemiology framework and employed the counterfactual framework of causation [26]. The methodology adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [27].

Setting

Sleman Regency had 2272 documented stunting cases in 2024. The study focused on 6 subdistricts (Sleman, Brebah, Mlati, Kalasan, Godean, and Tempel), accounting for 91.6% of the regency's stunting cases. Data were collected from the following:

1. Maternal medical records from public health centers
2. Maternal and child health (MCH) handbooks
3. Monthly integrated health post reports

Participants

The study population consisted of children aged 12 to 59 months registered in the district Integrated Nutrition Information System in 2024.

Eligibility Criteria

Inclusion criteria were as follows:

- Age 12 - 59 months
- Complete MCH handbook with documented pregnancy history
- Complete medical records from prenatal care
- Complete anthropometric data

Exclusion criteria were as follows:

- Congenital anomalies
- Chronic diseases affecting growth
- Incomplete pregnancy history data
- Missing anthropometric measurements

Sampling Strategy

A multistage cluster sampling method was used to obtain a representative sample of children aged 12 to 59 months in Sleman Regency. The process involved three stages.

Stage 1: Stratification of Subdistricts

Subdistricts were stratified based on the documented number of stunting cases:

- High burden: >400 stunting cases
- Medium burden: 200 - 400 stunting cases
- Low burden: <200 stunting cases

Stage 2: Random Selection of Subdistricts

Two subdistricts were randomly selected from each stratum:

- High: Sleman (634 cases) and Berbah (445 cases)
- Medium: Mlati (400 cases) and Kalasan (271 cases)
- Low: Godean (196 cases) and Tempel (135 cases)

Stage 3: Probability Proportional to Size Sampling

For the final stage, we established a comprehensive sampling frame consisting of all 150 active integrated health posts within the 6 selected subdistricts, based on the registry from the Sleman District Health Office. From this list, we used probability proportional to size sampling to randomly select 33 integrated health posts, where the probability of selection was proportional to the number of children aged 12 to 59 months registered at each integrated health post.

Within each of the 33 selected integrated health posts, a systematic random sampling technique was used to recruit participants. The monthly attendance register of children aged 12 to 59 months served as the sampling frame. We calculated a fixed sampling interval (k) and aimed to recruit approximately 30 eligible children from each integrated health post until the target initial sample size of 990 children was achieved ($33 \text{ integrated health post} \times 30 \text{ children/integrated health post} = 990$). This approach ensured that the final sample was proportional to the population distribution across the selected subdistricts and that the recruitment process was both systematic and random.

Participant Flow

A total of 990 eligible respondents were recruited from 6 subdistricts and 33 integrated health posts. However, due to incomplete data, 540 respondents were excluded. The final analytical sample comprised 450 children (300 children with stunting and 150 children without stunting).

Sample Size Calculation

Using the formula for estimating a proportion in a finite population ($N=62,817$, $Z=1.96$, $p=0.50$, $e=0.046$), a total sample size of 450 children was determined [28].

Variables

Dependent Variable

Stunting (height-for-age z score ≤ -2 SD; WHO 2006) is the dependent variable of the study.

Independent Variable

HRP complications (with timing of assessment) is the independent variable, including:

- Anemia: Diagnosed based on hemoglobin levels ($Hb < 11$ g/dL) recorded during the first trimester (≤ 13 wk) and/or third trimester (≥ 28 wk) of pregnancy as documented in the MCH handbook, following WHO guidelines [22].
- Preeclampsia: Identified by new-onset hypertension ($BP \geq 140/90$ mmHg) with proteinuria occurring after 20 weeks of gestation as per routine ANC monitoring records, in line with American College of Obstetricians and Gynecologists guidelines [25].
- GDM: Diagnosed based on an abnormal oral glucose tolerance test (OGTT) result conducted between 24 and 28 weeks of gestation, using the International Association of Diabetes and Pregnancy Study Groups criteria [29].
- Heart disease: Documented preexisting or pregnancy-induced cardiac conditions diagnosed at any point during pregnancy and recorded in medical records, as defined by standard obstetric practice [25].
- Asthma: Physician-diagnosed asthma with exacerbations recorded during the pregnancy period in the MCH handbook or medical records, following the Global Initiative for Asthma report [30].
- HRP categorized as none, single, and multiple (≥ 2).

Confounding Variables

Maternal age, education, family income, ANC visits, iron consumption, maternal nutrition, and family size

Maternal Nutrition (Operational Definition)

Maternal nutritional status was assessed using prepregnancy or first-trimester BMI documented in the MCH handbook. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). For this study, "inadequate maternal nutrition" was defined as a BMI less than 18.5 kg/m^2 (underweight), as this represents a state of chronic undernutrition strongly linked to adverse pregnancy outcomes, following WHO classifications [31].

Data Collection and Quality Assurance

Data were collected through a rigorous three-step process to ensure validity and minimize bias: (1) medical record review for HRP history and maternal variables, (2) MCH handbook review for detailed pregnancy history and ANC visits, and (3) direct verification of anthropometric data at integrated health posts.

Quality Control and Measurement Validity

To ensure the highest data quality, a comprehensive quality assurance protocol was implemented.

- Training and standardization: All field staff responsible for data extraction and anthropometric measurements underwent a 3-day intensive training workshop prior to data collection. This included standardization exercises for both data abstraction and height measurement techniques, as recommended by the Demographics and Health Surveys Phase 8 Anthropometry Manual [32]. An inter-rater

reliability assessment was conducted, showing high agreement ($\kappa=0.89$). A refresher training session was also held midway through the data collection period to prevent observer drift.

- Anthropometric measurement protocol: A child's height was measured using a Seca 213 microtoise (precision: 0.1 cm). Two measurements were taken and averaged if the difference was less than 0.5 cm. All procedures strictly followed WHO protocols [1].
- Instrument calibration: The Seca 213 microtoise was calibrated for accuracy daily before the first measurement using a standard calibrated measuring rod by the field supervisor. Any instrument deviating by more than 0.1 cm was immediately replaced, a critical step for ensuring measurement validity [33].

Statistical Analysis

Data were analyzed using Python (pandas 1.5.3, numpy 1.24.3, scipy 1.10.1; Integrated Development Environment). Descriptive statistics were presented as means with SD for continuous variables and frequencies with percentages for categorical variables. Bivariate analyses, including χ^2 tests for categorical variables and t tests for continuous variables, were conducted to examine the unadjusted associations between independent variables and stunting, reporting unadjusted odds ratios (OR) with 95% CI. A multivariate logistic regression model was developed to determine the independent association between HRP complications and stunting while controlling for confounders. All identified confounding variables (maternal age, education, family income, ANC visits, iron tablet

consumption, maternal nutrition, and family size) were entered into the model simultaneously using a forced entry method. The model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test, Nagelkerke R^2 , and the area under the receiver operating characteristic curve. A 2-tailed P value less than .05 was considered statistically significant.

Ethical Considerations

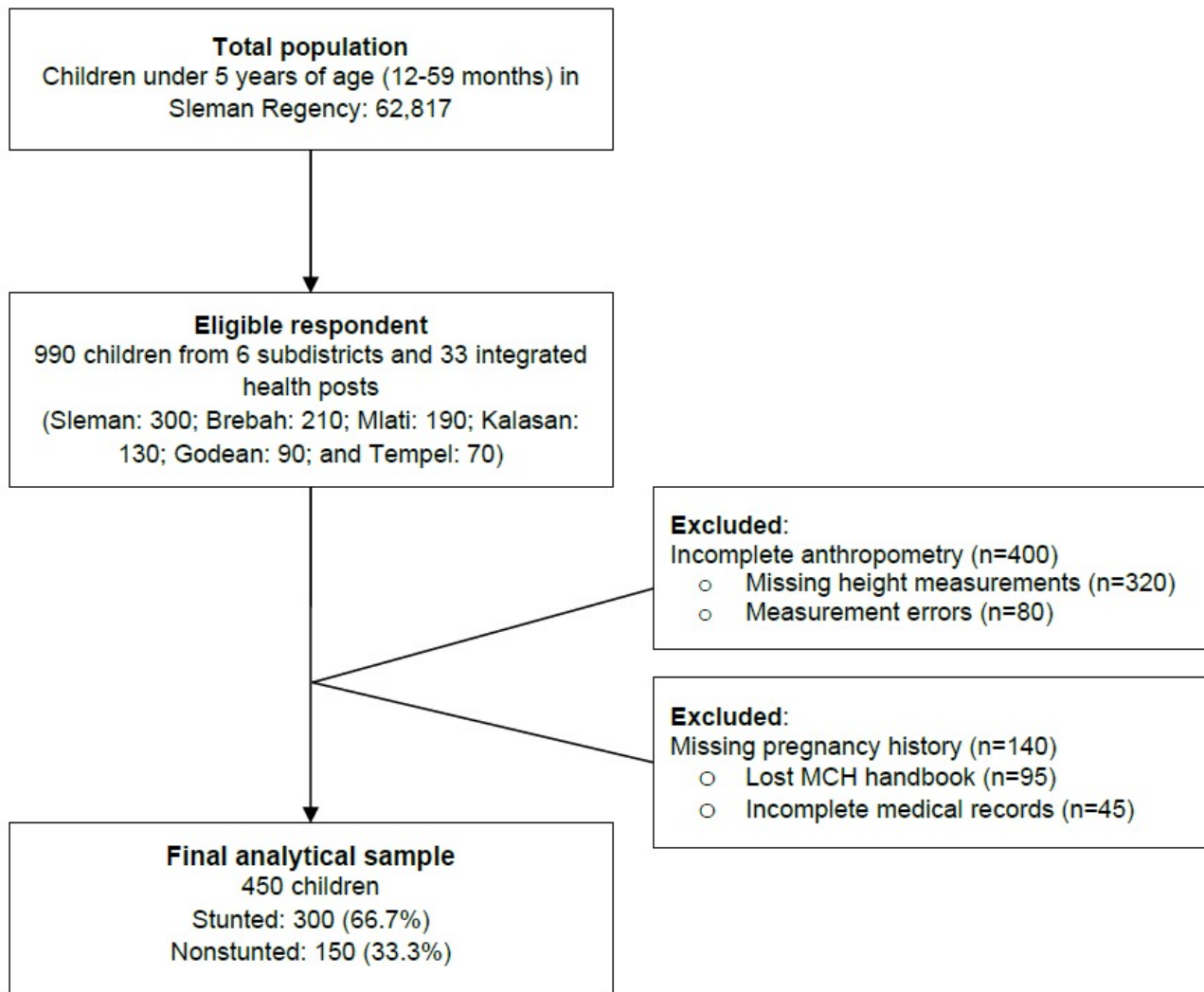
Ethical approval was obtained from the Ethics Committee Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (Ref: KE/FK/0825/EC/2025). All data were anonymized to protect respondents' privacy and confidentiality. Since this study was using retrospective data, informed consent was not needed. The study was conducted in accordance with the Declaration of Helsinki [34] and relevant bioethical principles [35].

Results

Participant Flow

The participant selection process is detailed in [Figure 1](#). From an initial pool of 990 children recruited from the selected integrated health posts, a total of 540 children were excluded due to incomplete data. The primary reasons for exclusion were incomplete anthropometric measurements ($n=400$) and incomplete pregnancy history data ($n=140$), which were treated as mutually exclusive categories. This resulted in a final analytical sample of 450 children (300 children with stunting and 150 without stunting).

Figure 1. Flow diagram of participant selection in Sleman Regency, Indonesia. MCH: maternal and child health.



Characteristics of Study Participants

The final sample of 450 children was drawn from 6 subdistricts, with the number of participants from each stratum being proportional to the documented stunting cases (high: Sleman

and Berbah; medium: Mlati and Kalasan; and low: Godean and Tempel). The distribution of children with and without stunting across these subdistricts was comparable ($P=.87$). The characteristics of the study participants are presented in [Table 1](#).

Table . Comparison of child and maternal characteristics between children with stunting (n=300) and those without stunting (n=150) in Sleman Regency, Indonesia.

Variable and category	Children with stunting (n=300)	Children without stunting (n=150)	P value
Child characteristics			
Age (mo), mean (SD)	34.8 (12.9)	34.1 (12.6)	.43
Sex, n (%)			.68
Female	142 (47.3)	74 (49.3)	
Male	158 (52.7)	76 (50.7)	
Maternal characteristics			
Education, n (%)			<.001
No education	15 (5.0)	3 (2.0)	
Elementary school	35 (11.7)	8 (5.3)	
Junior high school	85 (28.3)	18 (12.0)	
Senior high school	149 (49.7)	99 (66.0)	
College/university	16 (5.3)	22 (14.7)	
Family income (IDR ^a), n (%)			<.001
Low (<1.5 million)	187 (62.3)	52 (34.7)	
Medium (1.5 - 3 million)	89 (29.7)	68 (45.3)	
High (>3 million)	24 (8.0)	30 (20.0)	
ANC ^b visits, n (%)			<.001
<6 visits	98 (32.7)	21 (14.0)	
≥6 visits	202 (67.3)	129 (86.0)	
Iron tablets, n (%)			<.001
<90 tablets	176 (58.7)	48 (32.0)	
≥90 tablets	124 (41.3)	102 (68.0)	
Maternal nutrition, n (%)			<.001
Inadequate	193 (64.3)	43 (28.7)	
Adequate	107 (35.7)	107 (71.3)	
Family size, n (%)			<.001
≤4 members	98 (32.7)	89 (59.3)	
>4 members	202 (67.3)	61 (40.7)	

^aUS \$1=16,740.00 IDR.

^bANC: antenatal care.

Table 1 presents participant characteristics and the sampling process. The mean age was 34.6 (SD 12.8) months, with no significant difference between stunted (34.8, SD 12.9 mo) and nonstunted (34.1, SD 12.6 mo) groups ($P=.43$). Gender distribution was similar (158/300, 52.7% male in stunted group vs 76/150, 50.7% in nonstunted group; $P=.68$). Significant differences were observed in maternal education ($P<.001$), family income ($P<.001$), ANC visits ($P<.001$), iron supplementation ($P<.001$), maternal nutrition ($P<.001$), and family size ($P<.001$).

Prevalence of HRP Complications

Table 2 shows the prevalence of HRP complications. Any HRP complication was significantly higher among mothers of children with stunting (206/300, 68.7% vs 48/150, 32%; $P<.001$). Anemia was the most common complication (145/300, 48.3% vs 34/150, 22.7%, $P<.001$), followed by preeclampsia (46/300, 15.3% vs 6/150, 4%; $P<.001$). A clear dose-response relationship was observed: children exposed to multiple HRP complications had 6.71 times higher odds of stunting (OR 6.71, 95% CI 3.54 - 12.72).

Table . Prevalence of individual and cumulative high-risk pregnancy (HRP) complications among mothers of children with and without stunting, with unadjusted odds ratios (ORs) for stunting.

HRP component	Children with stunting (n=300)	Children without stunting (n=150)	Unadjusted OR (95% CI)	P value
Any HRP, n (%)	206 (68.7)	48 (32.0)	4.67 (3.10 - 7.04)	<.001
Individual complications, n (%)				
Anemia (Hb ^a <11 g/dL)	145 (48.3)	34 (22.7)	3.17 (2.10 - 4.78)	<.001
Preeclampsia	46 (15.3)	6 (4.0)	4.33 (1.83 - 10.24)	<.001
Gestational diabetes	28 (9.3)	7 (4.7)	2.07 (1.01 - 4.25)	.05
Heart disease	12 (4.0)	2 (1.3)	3.08 (0.68 - 13.94)	.09
Asthma	18 (6.0)	5 (3.3)	1.86 (0.69 - 5.01)	.16
Number of HRP complications, n (%)				
None	94 (31.3)	102 (68.0)	Reference	<u>—</u> ^b
One complication	132 (44)	36 (24.0)	3.98 (2.49 - 6.36)	<.001
Two or more complications	74 (24.7)	12 (8.0)	6.71 (3.54 - 12.72)	<.001

^aHb: hemoglobin.^bNot applicable.

Bivariate and Multivariate Analysis

Table 3 presents bivariate and multivariate analysis results. After adjustment for all confounders, anemia (adjusted OR [aOR] 3.21, 95% CI 2.12 - 4.86), preeclampsia (aOR 4.37, 95% CI 2.18 - 8.76), and gestational diabetes (aOR 2.85, 95% CI 1.42 - 5.72) remained significantly associated with stunting.

Children exposed to multiple HRP complications showed a 5.8-fold increased risk (aOR 5.80, 95% CI 3.26 - 10.32). Among confounders, maternal education (aOR 0.72, 95% CI 0.58 - 0.89), family income (aOR 0.68, 95% CI 0.52 - 0.89), and ANC visits (aOR 0.85, 95% CI 0.76 - 0.95) were independently protective (Figure 2).

Table . Bivariate and multivariate logistic regression analysis of factors associated with stunting in children aged 12 - 59 months (n=450)^a.

Variable	Unadjusted OR ^b (95% CI)	P value	aOR ^c (95% CI)	P value
HRP^d complications				
Anemia (Hb ^e <11 g/dL)	3.17 (2.10 - 4.78)	<.001	3.21 (2.12 - 4.86)	<.001
Preeclampsia	4.33 (1.83 - 10.24)	<.001	4.37 (2.18 - 8.76)	<.001
Gestational diabetes	2.07 (1.01 - 4.25)	.05	2.85 (1.42 - 5.72)	.003
Heart disease	3.08 (0.68 - 13.94)	.09	2.63 (0.57 - 12.14)	.22
Asthma	1.86 (0.69 - 5.01)	.16	1.74 (0.63 - 4.79)	.29
Number of HRP complications				
None	Reference	<u>f</u>	Reference	—
One complication	3.98 (2.49 - 6.36)	<.001	3.45 (2.14 - 5.56)	<.001
Two or more complications	6.71 (3.54 - 12.72)	<.001	5.80 (3.26 - 10.32)	<.001
Confounding factors				
Maternal age (per year increase)	0.98 (0.94 - 1.02)	.34	1.01 (0.96 - 1.06)	.73
Maternal education (per level increase)	0.65 (0.52 - 0.81)	<.001	0.72 (0.58 - 0.89)	.003
Family income (per category increase)	0.58 (0.45 - 0.75)	<.001	0.68 (0.52 - 0.89)	.005
ANC ^g visits (per visit increase)	0.79 (0.71 - 0.88)	<.001	0.85 (0.76 - 0.95)	.006
Iron tablet consumption (<90 vs ≥90)	3.01 (2.03 - 4.47)	<.001	1.21 (0.75 - 1.95)	.43
Maternal nutrition (inadequate vs adequate)	4.47 (2.98 - 6.71)	<.001	1.34 (0.81 - 2.21)	.25
Family size (per person increase)	1.42 (1.23 - 1.64)	<.001	1.08 (0.92 - 1.27)	.34

^aModel fit statistics: Hosmer-Lemeshow test: $\chi^2=6.84$, $P=.55$; Nagelkerke $R^2=0.412$; area under receiver operating characteristic curve 0.812. Key finding: Multiple HRP complications (≥ 2) showed the strongest association with stunting (aOR 5.80), exceeding individual risks like anemia (aOR 3.21) or preeclampsia (aOR 4.37).

^bOR: odds ratio.

^caOR: adjusted odds ratio.

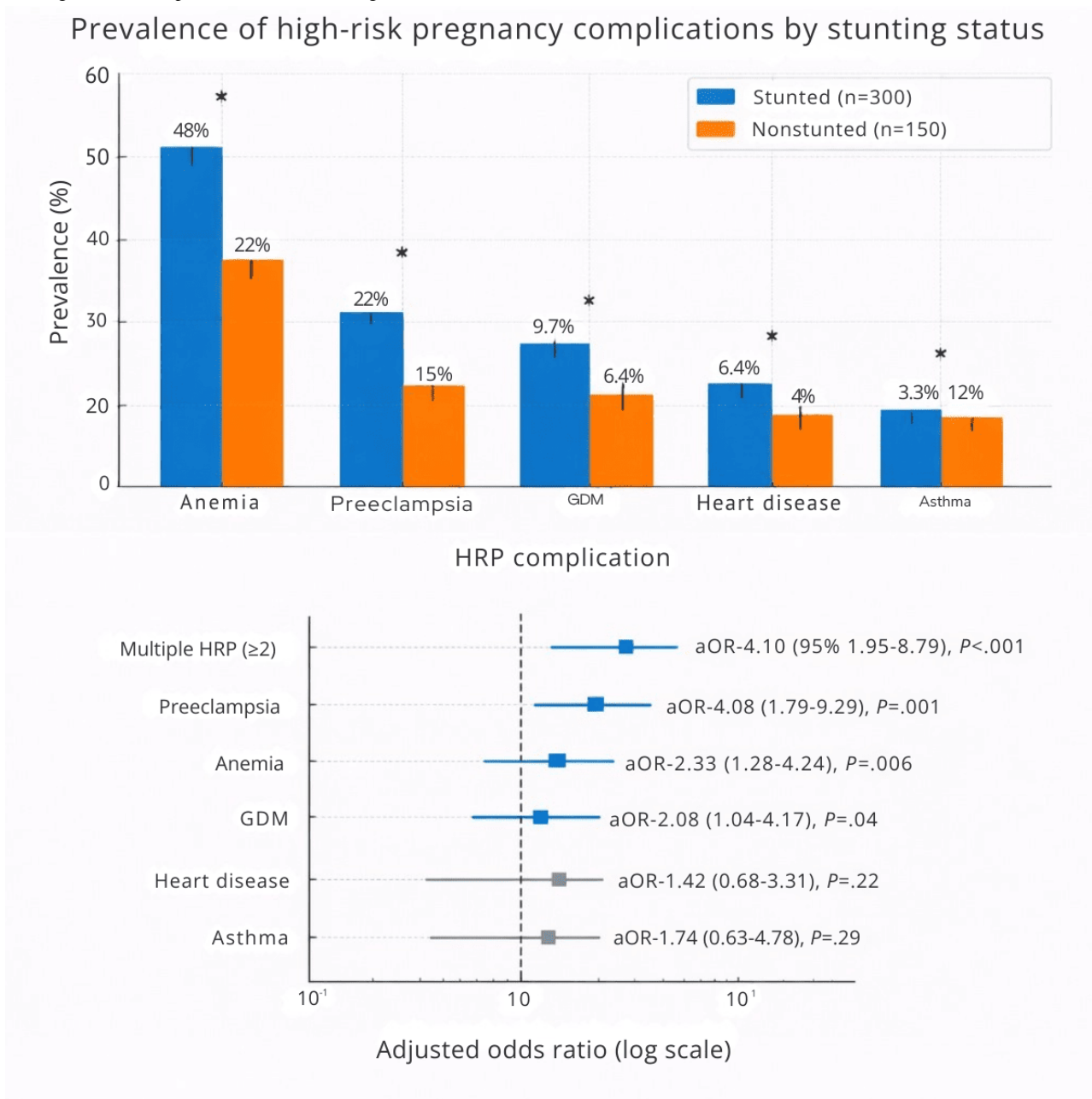
^dHRP: high-risk pregnancy.

^eHb: hemoglobin.

^fNot applicable.

^gANC: antenatal care.

Figure 2. Adjusted odds ratios (aOR) from multivariate logistic regression showing the association between high-risk pregnancy (HRP) complications and stunting. Error bars represent 95% CIs. GDM: gestational diabetes mellitus.



Model Fit Statistics

The multivariate model showed good fit (Hosmer-Lemeshow test: $\chi^2=6.84, P=.55$; Nagelkerke $R^2=0.412$; area under receiver operating characteristic curve=0.812) with no multicollinearity (all variance inflation factor <2.5).

Discussion

Main Findings and Theoretical Implications

This study provides compelling evidence that the cumulative burden of HRP complications, rather than isolated conditions, is the most powerful prenatal factor associated with stunting in Indonesian children. Our finding of a dose-response relationship, where exposure to two or more HRP complications increased stunting risk nearly 6-fold (aOR 5.80), offers strong empirical

support for the DOHaD hypothesis [16]. Critically, our findings extend the DOHaD framework by demonstrating that it is not merely the presence of a single prenatal insult but the synergistic interaction of multiple simultaneous exposures that most profoundly disrupts fetal programming and elevates disease risk later in life [10,11,16]. This challenges the current ANC paradigm in Indonesia, which predominantly focuses on identifying and managing single risks like anemia or preeclampsia, potentially overlooking pregnancies with overlapping complications that confer substantially higher risk.

While anemia and preeclampsia remained significant independent predictors, their impact must be contextualized within the broader landscape of cumulative risk. Anemia (aOR 3.21) was the most prevalent single complication in our study (48.3% in the stunted group), consistent with Indonesia’s high national maternal anemia burden of 48.9% [12]. However, its

effect size was substantially lower than that of multiple HRP exposures. Similarly, preeclampsia (aOR 4.37), while strongly associated, was also outpaced by the combined risk. These findings indicate that isolated management of single risks during ANC may miss HRPs with overlapping complications, underscoring the need to understand the synergistic biological pathways that make the cumulative effect so profound.

Biological Mechanisms of Cumulative Risk

Our finding that multiple HRP complications exponentially increase stunting risk suggests synergistic biological effects rather than a simple additive model. According to the DOHaD framework, the fetus adapts to the intrauterine environment. However, multiple simultaneous stressors can overwhelm these adaptive mechanisms, leading to permanent alterations in developmental programming. Several interconnected pathways likely explain this phenomenon. First, placental dysfunction serves as a central hub. Conditions like preeclampsia directly impair placental blood flow, a process increasingly understood through specific placental biomarkers that predict adverse outcomes [36], leading to fetal hypoxia and nutrient restriction. When combined with maternal anemia, which reduces the oxygen-carrying capacity of the blood, the placenta's ability to deliver oxygen and nutrients is severely compromised, amplifying fetal growth restriction [19]. Second, oxidative stress and inflammation are common final pathways for many HRP complications. Preeclampsia, GDM (through hyperglycemia), and anemia (through hypoxia-reperfusion injury) all independently increase the production of reactive oxygen species. The concurrent presence of these conditions creates a pro-inflammatory and prooxidant intrauterine environment that can damage developing fetal tissues and disrupt metabolic programming [37]. Finally, the combined metabolic disruption is critical. For instance, a fetus exposed to both maternal anemia (nutrient deprivation) and GDM (excess glucose) receives conflicting and damaging signals, forcing it to adapt to both scarcity and toxicity simultaneously. This metabolic dissonance can have a more profound impact on endocrine and cardiovascular system development than either condition alone, setting the stage for postnatal growth faltering and stunting [38].

Role of Socioeconomic and Health Care Factors

While the biological mechanisms explain the heightened vulnerability from cumulative HRP exposures, our analysis also identified key protective factors. Maternal education (aOR 0.72), family income (aOR 0.68), and ANC visits (aOR 0.85) were significantly associated with reduced stunting risk. However, their modest effect sizes reveal a complex reality and highlight the limitations of current interventions. This complexity is further illustrated by the shifting significance of iron tablet consumption and maternal nutrition. Both showed strong associations in bivariate analysis but lost significance after adjustment for socioeconomic confounders, suggesting their effects are largely mediated by upstream factors like education and income [26]. It appears that mothers with higher education and greater resources are better equipped to maintain adequate nutrition and adhere to supplementation, positioning these socioeconomic conditions as more fundamental determinants of child growth [3,14]. This finding underscores that

interventions focusing solely on nutrient provision or increasing ANC visit frequency, without addressing the underlying socioeconomic context, are likely to have limited long-term impact on stunting prevention.

Strengths

This study has several methodological strengths. First, the large, representative sample with rigorous multistage cluster sampling enhances external validity. Second, comprehensive adjustment for socioeconomic and health care confounders strengthens our analytical approach. Third, the use of contemporary international guidelines [22,25] for HRP diagnosis ensures methodological rigor and comparability. Fourth, triangulation of multiple data sources minimizes misclassification bias. Fifth, the application of advanced statistical methods with appropriate model fit assessment ensures the robustness of our findings.

Limitations

Despite these strengths, several limitations must be acknowledged. Our interpretation of the findings is constrained by the study's retrospective observational design and data sources, which also impact the generalizability of our results.

- **Study design and causality:** The retrospective, cross-sectional nature of our analysis limits our ability to establish temporality and infer direct causality. While we have identified strong and statistically significant associations, we cannot confirm that the observed HRP complications directly caused stunting, only that they are robustly linked within the DOHaD framework.
- **Potential for selection bias:** A significant limitation is the exclusion of 540 participants (54.5% of the initial sample) due to incomplete data. This raises a substantial risk of selection bias. It is plausible that mothers and children excluded from the analysis faced greater socioeconomic challenges or more severe health complications, which could lead to an overestimation of the effect sizes reported. Future research should implement more robust data collection strategies to minimize exclusions and ensure findings are more generalizable.
- **Data constraints and unmeasured mediators:** Our reliance on secondary data from medical records and MCH handbooks, while practical, is subject to potential inaccuracies in documentation. Furthermore, we could not assess the severity or gestational timing of HRP complications, which may have differential impacts. Critically, our dataset did not include key perinatal and postnatal mediators such as birth weight, gestational age, and breastfeeding practices that are central to the DOHaD framework. Consequently, we are unable to quantify the indirect effects of HRP and can only report the total effect, not the specific direct and indirect pathways. For instance, birth weight and gestational age are critical outcomes of a complicated pregnancy and are themselves strong predictors of stunting [7]. Similarly, breastfeeding practices (eg, exclusivity and duration) can be influenced by maternal health and are a major determinant of postnatal growth [7]. Future research should aim to integrate these perinatal and postnatal variables to provide a more complete

understanding of the DOHaD mechanisms in this context [9].

- Generalizability of findings: This study was conducted in Sleman Regency, a region with relatively high development indices and health care access compared to many high-burden areas in Indonesia, such as Central Papua [5,39]. Therefore, while the fundamental biological relationship between cumulative HRP and stunting is likely universal [10], the specific prevalence and effect sizes observed may not be directly generalizable to less-resourced settings. Our findings are most directly applicable to similar regencies in Java, and they serve as a crucial call for further research in more diverse contexts.

Implications for Policy and Practice

Our findings align with studies from other LMICs showing strong associations between maternal HRP and child stunting. A recent systematic review by Beal et al [20] reported similar effect sizes for anemia and preeclampsia in Indonesian children. However, our study adds significant value by being the first to examine multiple HRP complications simultaneously, demonstrating their synergistic cumulative effect while controlling for a comprehensive set of confounders using contemporary international guidelines [22,25].

The Indonesian context presents unique challenges and variations. In our study area of Sleman, anemia prevalence was high (48.3%), yet the national stunting burden shows stark disparities, from 7.2% in Bali to 39.4% in Central Papua [4,5], a pattern where the latest analyses confirm that socioeconomic factors remain a primary driver of stunting nationally [13,40]. This complex landscape, characterized by a dual burden of malnutrition and epidemiological transition, underscores why a single-risk approach is insufficient. Our analysis demonstrates that cumulative risk assessment better predicts stunting in this diverse environment.

Given this robust evidence, our findings have direct and critical implications for MCH policy in Indonesia. The current single-risk-focused ANC paradigm is insufficient to address the complex, cumulative risks we have identified. We recommend the following actionable shifts:

- Revise ANC protocols to incorporate cumulative risk assessment: National guidelines should be updated to include a cumulative risk scoring system. Pregnancies with two or more identified HRP complications should be automatically flagged as “very high risk” and prioritized for intensive, integrated management involving both obstetricians and nutritionists.

- Integrate MCH services: To break the intergenerational cycle of malnutrition, health information systems must be linked. A mother’s history of cumulative HRP complications should trigger targeted postnatal follow-up for her infant, including enhanced growth monitoring and nutritional support, regardless of the infant’s initial anthropometric status.
- Strengthen health system capacity: Addressing cumulative risk requires a well-trained and empowered workforce. Investment in training for ANC providers to identify, manage, and counsel patients with multiple complications is essential. This includes training on the DOHaD framework to enhance their understanding of the long-term implications of prenatal care quality.

Strengthen health system Capacity: Addressing cumulative risk requires a well-trained and empowered workforce. Investment in training for ANC providers to identify, manage, and counsel patients with multiple complications is essential. This includes training on the DOHaD framework to enhance their understanding of the long-term implications of prenatal care quality.

By adopting a cumulative risk framework aligned with the DOHaD hypothesis, Indonesia can accelerate progress toward reducing stunting and breaking the cycle of intergenerational malnutrition.

Research Recommendations

Prospective cohort studies are needed to establish temporality and explore mediating pathways in the HRP-stunting relationship. Implementation research on integrated HRP-stunting prevention programs could identify effective delivery strategies. Finally, exploration of biological mechanisms could advance our understanding of developmental programming and identify novel intervention targets.

Conclusion

In conclusion, this study provides compelling evidence that the cumulative burden of HRP complications is the most powerful factor associated with stunting in Indonesian children. While individual complications remain significant, their impact is substantially lower than that of cumulative exposures. This challenges the current single-risk-focused ANC paradigm and highlights the urgent need for a shift toward integrated, cumulative risk management strategies. Such a paradigm shift, aligned with the DOHaD framework, is essential for effectively breaking the intergenerational cycle of malnutrition in Indonesia.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to respondents’ privacy but are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: WW

Methodology: WW

Writing – original draft: WW

Data analysis: WW

Data curation: HMR

Formal analysis: HMR

Investigation: HMR

Writing: HMR

Review and editing: WW, HMR

Conflicts of Interest

None declared.

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Abbreviations

- ANC:** antenatal care
aOR: adjusted odds ratio
DOHaD: Developmental Origins of Health and Disease
GDM: gestational diabetes mellitus
HRP: high-risk pregnancy
LMICs: low- and middle-income countries
MCH: maternal and child health
OR: odds ratio

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

WHO: World Health Organization

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Differential Association of Inflammation With Pain and Physical Function in Knee Osteoarthritis by Race Focusing on Non-Hispanic Whites and Asian Americans: Pilot Study in Florida

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Abstract

Background: The current body of work has not yet addressed the potential racial differences in the relationship between systemic inflammation and knee osteoarthritis (OA) symptoms, including pain and physical function.

Objective: This pilot study aimed to investigate this association specifically among non-Hispanic Whites and Asian Americans.

Methods: We cross-sectionally analyzed 40 community-dwelling participants aged 50 - 70 years with self-reported knee OA pain, including 20 non-Hispanic Whites and 20 Asian Americans. Knee OA symptoms were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales. The serum levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), and interleukin-10, as systemic inflammatory markers, were measured. Univariate and multivariable analyses, using stepwise linear regression models, were conducted to examine the correlation between these inflammatory markers and OA symptoms, with systematic adjustment for age.

Results: In non-Hispanic Whites, the above inflammatory markers did not correlate with knee pain or physical function. In Asian Americans, bivariate analyses revealed that CRP and TNF- α levels were associated with worse WOMAC pain scores ($r=1.325$, $P=.041$; and $r=2.418$, $P=.036$, respectively), and CRP levels were also linked to worse WOMAC physical function scores ($r=4.950$, $P=.035$). Multivariate analyses confirmed the association of CRP levels with both worse WOMAC pain ($\beta=1.328$, $P=.046$) and physical function ($\beta=4.974$, $P=.034$) scores in Asian Americans.

Conclusions: CRP may be a clinically relevant marker for knee OA symptoms, specifically in Asian Americans; however, caution is warranted owing to the exploratory nature of this study. Future research is set to benefit from leveraging a larger sample, incorporating additional inflammatory markers, and including racially diverse samples to validate and augment these findings.

Trial Registration: Clinicaltrials.gov NCT02512393; <https://www.clinicaltrials.gov/study/NCT02512393>

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KEYWORDS

Asian Americans; inflammation; knee osteoarthritis; pain; physical function

Introduction

Background

Knee osteoarthritis (OA) is one of the leading causes of pain, daily living impairments, and disability in people aged ≥ 45 years. Although local inflammation aggravates OA joint pathologies, systemic inflammatory markers are also elevated in OA, especially in the presence of symptoms such as pain and reduced physical function [1,2]. Notwithstanding, the evidence remains controversial. The pooled results of a meta-analysis indicated a weak correlation between serum C-reactive protein (CRP) levels and knee OA pain [1]. Other studies have identified no significant association between serum CRP levels and knee OA pain or physical function [3,4]. A recent systematic review

also reported conflicting associations of other markers, such as interleukin (IL)-6, with pain scores in patients with knee OA [5].

Several researchers argue that inconsistent evidence regarding the relationship between inflammation and knee OA symptoms is attributable to sex-specific differences [6-8]. However, considerably less attention has been focused on the possibility of racial/ethnic disparities in these relationships. Racial/ethnic minority groups, owing to systemic inequities and environmental challenges, may develop a different inflammatory fingerprint than their non-Hispanic White counterparts (ie, epigenetics) [9]. They are also disproportionately susceptible to chronic knee OA pain [10-12]. Nonetheless, most studies on inflammation and knee OA symptoms have failed to specify the racial

composition of their samples, predominantly included non-Hispanic White participants, or adopted typical approaches that report average effects from race/ethnicity-adjusted analyses, possibly obscuring crucial dissimilarities. Overlooking such differences potentially hinders the development of personalized approaches to analgesic care and interventions that improve physical function, ultimately impeding efforts to reduce pain inequities across groups.

To our knowledge, no study has elucidated the potential racial/ethnic differences in the relationship between systemic inflammatory markers and knee OA symptoms. Only recently, Overstreet et al [13] found that the expressions/profiles of biomarkers underlying inflammation associated with chronic low back pain-related outcomes (ie, pain interference, pain at rest, and movement-evoked pain) differed between non-Hispanic Whites and non-Hispanic Blacks.

Study Aim

This pilot study investigated the relationship between inflammation and knee OA symptoms (ie, pain and physical function) by race. Specifically, we compared non-Hispanic Whites to Asian Americans. Asian Americans constitute a rapidly growing minority yet have been underrepresented in knee OA research, despite emerging evidence indicating that they experience greater knee OA symptoms than non-Hispanic Whites [10,11]. This underscores the critical importance of studying this population.

Methods

Study Design and Participants

This cross-sectional analysis used baseline data from a randomized controlled trial (RCT) registered at clinicaltrials.gov (NCT02512393) to assess the efficacy of transcranial direct current stimulation (tDCS) in mitigating knee OA pain. The parent trial employed a double-blind, sham-controlled, parallel-group design, in which participants were randomly assigned to receive either active tDCS (n=20) or sham tDCS (n=20). Participants underwent daily 20-minute stimulation sessions for 5 consecutive days. Additional details regarding the design and procedures of the parent RCT are reported elsewhere [14,15]. At baseline, a total of 40 individuals with self-reported knee OA pain (20 non-Hispanic Whites and 20 Asian Americans) were recruited in North Central Florida between September 2015 and August 2016. Prior to the intervention, participants completed comprehensive baseline assessments, including demographic characteristics, clinical measures, knee OA pain severity, physical function, and relevant biological factors. The breadth and depth of these baseline data provided a robust foundation for the present cross-sectional analyses.

Recruitment was conducted through a combination of posted flyers, email advertisements, and community-based outreach efforts at local clinics, hospital-based outpatient services, and community centers. Flyers and electronic announcements described the study purpose, eligibility criteria, and contact information for the research team. Interested individuals contacted the study staff and were provided with additional

information about the study. Some participants were recruited via direct referral from treating clinicians in outpatient settings. Potential participants then underwent a standardized screening process, which included an initial telephone screening followed by an in-person eligibility assessment to confirm the inclusion and exclusion criteria prior to enrollment.

Because the present analyses were conducted using baseline data from a parent RCT, the eligibility criteria reflected those of the parent trial rather than being tailored specifically for the current secondary analysis. Participants were eligible if they were aged 50 - 70 years; reported unilateral or bilateral knee OA pain according to the American College of Rheumatology criteria [16,17]; were able to speak and read English; were willing to be randomly assigned to either the intervention or control group; were available to complete five consecutive daily tDCS sessions and weekly follow-up phone assessments for 3 weeks; had no plans to change pain-related medication regimens during the study period; had no contraindications identified through the tDCS safety screening questionnaire (eg, epilepsy) [18]; and were willing and able to provide written informed consent prior to enrollment. Exclusion criteria ensured that participants did not have concurrent medical conditions that could confound OA-related outcomes or coexisting diseases that could hinder protocol completion. Thus, the following were the exclusion criteria: (1) having undergone prosthetic knee replacement or non-arthroscopic surgery on the affected knee, (2) a serious medical illness, such as uncontrolled hypertension, heart failure, or a recent history of acute myocardial infarction, (3) peripheral neuropathy, (4) systemic rheumatic disorders, such as rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia, (5) alcohol or substance abuse, (6) cognitive impairment, defined as a Mini-Mental Status Exam score of 23 or lower, (7) a history of brain surgery, tumor, seizure, stroke, or intracranial metal implantation, (8) pregnancy or lactation, and (9) hospitalization for a psychiatric illness within the past year.

Measurement

The collected basic characteristics included age, sex (male vs female), marital status (partnered vs unpartnered), BMI (kg/m²), and Kellgren–Lawrence (KL) radiographic grade (0 - 1 vs 2 - 4), pain catastrophizing, and negative affect. The study assessed pain catastrophizing using the pain catastrophizing scale (PCS), a 13-item measure designed to evaluate catastrophic thinking related to pain across three dimensions: rumination, magnification, and helplessness [19,20]. Each item was scored on a 5-point Likert scale ranging from “not at all” (0) to “all the time” (4). The PCS demonstrated adequate internal consistency, with subscale alphas ranging from 0.66 to 0.87 (α for all items=0.87) [19], and its sensitivity to psychosocial interventions for chronic pain has been well established [21]. Negative affect was assessed using the 10-item negative affect subscale of the Positive and Negative Affect Schedule (PANAS-NA) [22]. Respondents are asked to rate on a 5-point scale (1 = “very slightly or not at all”; 5 = “extremely”) their agreement with 10 descriptors of negative affect (afraid, ashamed, distressed, guilty, hostile, irritable, jittery, nervous, scared, and upset). The PANAS has been validated and

demonstrates reliability, with an alpha coefficient range of .84 to .87 for negative affect [23].

Knee OA Symptoms: Knee OA Pain and Physical Function

Knee OA pain and physical function were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales, where higher scores indicate greater pain and physical functional disability [24]. The pain subscale includes 5 items on a 5-point Likert scale (0 being none to 4 being extreme) measuring the pain severity during walking, climbing stairs, sleeping, resting, and standing. The participants' responses to the pain questions were summed up to derive an aggregated score of pain intensity (range 0 - 20). The physical function subscale asks patients to rate the degree of difficulty in accomplishing 17 activities of daily living on a 5-point scale (0 being none to 4 being extreme). The participants' responses were aggregated to produce a composite score of functional disability (range 0 - 68). The subscales in WOMAC demonstrate reliability and validity in evaluating knee OA in patients [24,25].

Inflammatory Markers

In this study, we also gathered data regarding the following inflammatory markers: CRP, tumor necrosis factor-alpha (TNF- α), IL-1 β , IL-6, and IL-10. Owing to substantial missing data (45.0% - 80.0%), we excluded IL-1 β and IL-6 from the current analysis. In the original study [15], blood samples were obtained prior to treatment initiation (ie, tDCS) on day 1 and after completing the fifth treatment on day 5. For our analysis, we utilized pre-treatment data acquired on day 1. Blood was drawn into ethylenediaminetetraacetic acid plasma tubes. Samples were inverted five times and stored on ice until further processing. Within 30 min of being collected, samples were centrifuged at 1600 \times g and 4°C for 15 min, aliquoted, and immediately stored in a -80°C freezer.

The plasma samples underwent solid-phase extraction using an OasisTM Hydrophilic-Lipophilic-Balanced (30 mg) 96-well plate along with a vacuum manifold (Waters Corp.), according to the manufacturer's protocol. Briefly, the plate was conditioned with acetonitrile and equilibrated twice with 0.1% trifluoroacetic acid (TFA) in high-performance liquid chromatography (HPLC)-grade water. Samples were acidified with 1% TFA (1:1) and loaded onto the plate. The plate was washed thrice with 0.1% TFA in HPLC-grade water. The samples were eluted in 60% acetonitrile/40% HPLC-grade water/0.1% TFA and dried in a Savant AES1010 Automatic Environmental SpeedVAC[®] w/VaporNet Radiant Cover (Thermo Fisher Scientific). Thereafter, they were reconstituted using the original sample volume in assay buffer.

Plasma CRP levels were measured in duplicate using enzyme-linked immunosorbent assays, following the manufacturers' instructions (cat# DCRP00, R&D Systems, Minneapolis, MN; cat# ADI-900 - 071, Enzo Life Sciences, Inc., Farmingdale, NY, respectively). For CRP, the average intra- and interassay CV values were <10.0% and <7.0%, respectively. TNF- α and IL-10 plasma levels were measured in triplicate using a commercial multiplex immunoassay kit

(cat# HCYTMAG-60K1; MilliporeSigma, Burlington, MA) and analyzed using the MILLIPLEX[®] Analyzer 3.1 xPONENT[®] System (Luminex Corporation). Data acquisition was accomplished using the same system and data analysis performed via MILLIPLEX[®] Analyst Software. Intra- and interassay CVs were <19.0% for all markers.

Statistical Analysis

Descriptive and comparative statistics were employed to determine sample characteristics. As the inflammatory markers were not normally distributed, log transformation was applied to mitigate skewness. When missing data were present (CRP, n=4), listwise deletion was performed, resulting in a streamlined dataset for analysis. Race-stratified analyses were conducted owing to an observed interaction between race and certain inflammatory markers, such as CRP (data not shown). We examined the relationships between BMI and each inflammatory marker, aiming to circumvent possible collinearity (since adiposity proves to be significantly associated with systemic inflammation), and specifically investigated their associations with knee OA symptoms. Multivariable linear regression models were used in the main analysis of each outcome.

Explanatory variables included age, sex, marital status, BMI, and KL radiographic grade, all of which potentially affect both inflammation and knee OA symptoms [26,27]. Pain catastrophizing and negative affect were also considered because of their relation to knee OA symptoms [28-30]. Candidate variables comprised those with $P < .200$ in bivariate analyses: single-factor analysis of variance in cases of variance equality, the Kruskal-Wallis test for qualitative variables, and the simple linear regression test for quantitative variables. Multivariable analysis based on stepwise selection at an alpha value of .05 was conducted to preserve the most relevant variables in the model and distinguish those independently associated with the outcomes. In all multivariable models, systematic adjustment for age was performed. Finally, we conducted diagnostic tests to ensure that the multivariable models satisfied linear regression model assumptions. All statistical analysis was carried out using R Studio (version 4.0.2; R Foundation for Statistical Computing) [31].

Ethical Considerations

The Institutional Review Board (IRB) of the University of Arizona considers investigators engaged in research if (1) they interact with participants for research purposes; (2) they have access to identifying study information; (3) they obtain informed consent from research participants; or (4) the University of Arizona directly receives part of federal funds for the study (ie, the University of Arizona is the prime awardee). If none of the above are true, then the researchers would not require IRB approval. Thus, this secondary analysis of deidentified data from an existing RCT was determined to be exempt from IRB review. Informed written consent was obtained from all participants in the parent trial, and participants were compensated for their time and participation.

Results

Table 1 presents the characteristics of the participants by race. The groups differed in terms of age, BMI, KL radiographic grade, and pain catastrophizing. Asian American participants were significantly younger than non-Hispanic White participants (mean [SD] 54.80 [7.74] vs 65.10 [7.41] years; $P=.001$) and had a lower BMI (mean [SD] 25.02 [3.59] vs 27.98 [3.28] kg/m²;

$P=.001$). A greater proportion of Asian Americans had lower KL radiographic grades (0 - 1) compared with non-Hispanic Whites (80% vs 25%; $P=.001$). Asian American participants also reported higher pain catastrophizing scores than non-Hispanic White participants (mean [SD] 1.33 [1.25] vs. 0.31 [0.74]; $P=.004$). There were no significant differences between the groups in the levels of CRP, TNF- α , and IL-10, or in any WOMAC subscales ($P>.05$).

Table . Comparison of basic characteristics, inflammatory markers, and WOMAC^a subscale scores between non-Hispanic Whites and Asian Americans (n=40).

Variables	Non-Hispanic Whites (n=20)	Asian Americans (n=20)	P value
Age (years), mean (SD)	65.10 (7.41)	54.80 (7.74)	.001 ^b
Sex, n (%)			.205
Male	12 (60)	7 (35)	
Female	8 (40)	13 (65)	
Marital status			.127 ^c
Married/partnered	13 (65)	18 (90)	
Nonmarried/unpartnered	7 (35)	2 (10)	
Body mass index, kg/m ² , mean (SD)	27.98 (3.28)	25.02 (3.59)	.001 ^b
Kellgren-Lawrence radiographic grade (grade 0 - 1)			.001 ^{c,b}
Grade 0 - 1	5 (25)	16 (80)	
Grade 2 - 4	15 (75)	4 (20)	
Pain catastrophizing scale score, range: 0 - 6; mean (SD)	0.31 (0.74)	1.33 (1.25)	.004 ^b
Negative affect scale score, range: 10 - 50, mean (SD)	14.00 (4.29)	20.15 (9.02)	.165
Inflammatory markers, mean (SD)			
C-reactive protein, ng/ml	2295.27 (3002.13)	1001.12 (898.91)	.114
Tumor necrosis factor- α , pg/ml	10.33 (5.56)	7.51 (3.67)	.067
Interleukin-10, pg/ml	8.38 (5.27)	6.78 (3.69)	.273
Clinical pain measures, mean (SD)			
WOMAC pain, range: 0 - 20	4.90 (2.61)	4.40 (2.74)	.559
WOMAC physical function, range: 0 - 68	16.50 (9.86)	13.6 (9.95)	.361

^aWOMAC: Western Ontario and McMaster Universities Osteoarthritis.

^bSignificant results.

^cFischer exact test.

Table 2 presents the relationships between BMI and inflammatory markers by race. Pearson correlation analyses showed no statistically significant associations between BMI and log-transformed CRP, TNF- α , or IL-10 in either non-Hispanic Whites or Asian Americans (all $P>.05$). Similarly, ANOVA analyses revealed no significant differences in

inflammatory marker levels across BMI categories in either group. These findings indicate that BMI was not strongly correlated with inflammatory markers in this sample and did not raise major concerns about multicollinearity in subsequent analyses, as shown in **Table 2**.

Table . Relationships between BMI and inflammatory markers by race (n=40).

	Non-Hispanic Whites (n=20)			Asian Americans (n=20)		
	log(CRP) ^a , ng/ml	log(TNF- α) ^b , pg/ml	log(IL-10) ^c , pg/ml	log(CRP), ng/ml	log(TNF- α), pg/ml	log(IL-10), pg/ml
Pearson correlation coefficient	0.179	-0.079	-0.190	0.364	0.292	0.218
<i>P</i> value	.507	.740	.421	.115	.212	.356
18.5≤BMI<25 ^d , mean (SD)	7.49 (1.53)	2.22 (0.59)	2.01 (0.71)	6.13 (0.91)	1.79 (0.62)	1.74 (0.64)
25≤BMI<30 ^e , mean (SD)	6.75 (0.54)	2.20 (0.33)	1.97 (0.71)	7.11 (0.79)	1.97 (0.38)	1.74 (0.33)
BMI≥30 ^f , mean (SD)	7.73 (0.73)	2.26 (0.64)	1.87 (0.82)	6.71 (1.07)	2.22 (0.57)	2.11 (0.67)
ANOVA <i>P</i> value	.194	.971	.929	.096	.551	— ^g

^aCRP: C-reactive protein.

^bTNF- α : tumor necrosis factor-alpha.

^cIL-10: interleukin-10.

^dNon-Hispanic Whites (n=5), Asian Americans (n=11).

^eNon-Hispanic Whites (n=9), Asian Americans (n=7).

^fNon-Hispanic Whites (n=6), Asian Americans (n=2).

^gnot applicable.

Table 3 presents the results of bivariate and multivariable analyses in both non-Hispanic Whites and Asian Americans. In non-Hispanic Whites, both analyses indicated that only pain catastrophizing was associated with worse WOMAC pain score and WOMAC physical function score ($P<.050$). In Asian Americans, bivariate analysis indicated that CRP and TNF- α levels were associated with a worse WOMAC pain score ($r=1.325$, $P=.041$; $r=2.418$, $P=.036$, respectively), while the CRP level was also related to a worse WOMAC physical

function score ($r=4.950$, $P=.035$). In multivariable analysis adjusting for age, only the CRP level was associated with a worse WOMAC pain score ($\beta=1.328$, $P=.046$) and a WOMAC physical function score ($\beta=4.974$, $P=.034$) in Asian Americans. Of note, the IL-10 level was not significantly associated with WOMAC pain or physical function scores in either non-Hispanic White or Asian American participants in bivariate or multivariable analyses.

Table . Bivariate and multivariable analyses (n=40).

	Non-Hispanic Whites (n=20)								Asian Americans (n=20)							
	WOMAC ^a pain				WOMAC physical function				WOMAC pain				WOMAC physical function			
	Bivariate analysis		Multivariable analysis		Bivariate analysis		Multivariable analysis		Bivariate analysis		Multivariable analysis		Bivariate analysis		Multivariable analysis	
	r	P value	β (SE) ^b	P value	r	P value	β (SE)	P value	r	P value	β (SE)	P value	r	P value	β (SE)	P value
Age	-0.133	.101	-.062 (0.058)	.304	-0.170	.592	.048 (0.283)	.868	0.030	.724	.032 (0.076)	.683	0.278	.360	.284 (0.266)	.300
Sex	0.043	.378	— ^c	—	0.108	.157	—	—	0.027	.488	—	—	0.001	.921	—	—
Marital status	0.037	.414	—	—	0.004	.802	—	—	0.013	.637	—	—	0.000	.931	—	—
BMI	0.211	.259	—	—	0.682	.335	—	—	0.029	.872	—	—	-0.144	.828	—	—
KL ^d radiographic grade	0.087	.207	—	—	0.002	.860	—	—	0.006	.754	—	—	0.001	.897	—	—
Pain catastrophizing	2.548	<.001 ^e	2.370 (0.572)	.001 ^e	7.115	.013 ^e	7.252 (2.764)	.018 ^e	0.478	.345	—	—	1.395	.449	—	—
Negative affect	-0.068	.631	—	—	-0.720	.167	—	—	0.130	.053	—	—	0.279	.269	—	—
lgCRP ^f , ng/ml	-1.035	.157	—	—	-2.789	.283	—	—	1.325	.041 ^e	1.328 (0.616)	.046 ^e	4.950	.035 ^e	4.974 (2.157)	.034 ^e
lgTNF-α ^g , pg/ml	-0.115	.930	—	—	-2.613	.596	—	—	2.418	.036 ^e	—	—	6.716	.118	—	—
log(IL-10) ^h , pg/ml	-0.861	.395	—	—	-4.158	.273	—	—	1.134	.349	—	—	2.297	.604	—	—

^a WOMAC: Western Ontario and McMaster Universities Osteoarthritis.

^bSE: standard error.

^cnot applicable.

^dKL: Kellgren-Lawrence.

^eSignificant results.

^fCRP: C-reactive protein.

^gTNF-α: tumor necrosis factor-alpha.

^hIL-10: interleukin-10.

Discussion

Principal Findings and Comparison With Previous Works

This pilot study investigated whether differences in the relationship between inflammation and knee OA symptoms (pain and physical function) exist between non-Hispanic Whites and Asian Americans. Our adjusted analyses indicated that the CRP level persists as a clinically relevant marker for both knee OA pain and functional disability in Asian Americans. The

findings emphasize that inflammatory underpinnings of knee OA symptoms potentially vary among specific racial groups, echoing the results of Overstreet et al [13], which focused on patients with chronic low back pain.

However, interpretation needs caution. The proportion of individuals with early-stage knee OA (KL radiographic grade 0 - 1) significantly differed between the two groups, with 25% and 80% of non-Hispanic Whites and Asian Americans falling into this category, respectively. Evidence suggests that in early-stage knee OA, inflammation is a major reason why

patients seek medical assistance in outpatient departments, and anti-inflammatory treatment may be more effective during this stage; in contrast, in late-stage knee OA, pain may not primarily originate from inflammation but rather from other sources that require further investigation [32], a phenomenon corroborated by our study. Furthermore, in the current study, men constituted 60% and 35% of the non-Hispanic White and Asian American samples, respectively. Although this sex composition was not statistically significant, a previous study has reported sex-specific relationships exhibiting weaker associations of CRP and TNF- α with knee pain among men [7]; this possibly, in part, explains our insignificant findings for non-Hispanic Whites.

The findings wherein no relationships were established between inflammatory markers and knee OA symptoms among non-Hispanic Whites aligns with an earlier study predominantly based on non-Hispanic White samples [3]. However, it contrasts with results reported by Zhu et al [33], who found serum CRP to be cross-sectionally and longitudinally associated with knee pain in patients with knee OA, as well as with other research reporting significant associations between knee OA pain and TNF- α [7,34,35]. Nonetheless, direct comparisons are challenging owing to the unknown racial composition of these studies, our pilot study's cross-sectional nature characterized by small sample sizes, varying socioeconomic and clinical characteristics across the study populations, and the multidimensional nature of pain assessed using various tools across the studies.

Notably, the IL-10 level was not associated with knee OA symptoms in either non-Hispanic White or Asian American participants. IL-10 is an anti-inflammatory cytokine that regulates immune homeostasis and may slow the progression of knee OA [36]. Several studies in knee OA have reported null or negative associations between IL-10 levels and clinical pain and function [7,37,38]. Imamura et al [37] found no relationship between serum IL-10 levels and WOMAC pain scores in individuals with painful knee OA and sensitization. Perruccio et al [7] reported that higher serum IL-10 levels were associated with lower WOMAC pain scores, regardless of sex. Similarly, Zhu et al [38] examined longitudinal associations between inflammatory and metabolic markers and WOMAC outcomes and found that an IL-10-related component, characterized by predominantly anti-inflammatory markers, was negatively associated with WOMAC pain and function scores. Yet, none of the aforementioned studies examined racial differences in the associations between IL-10 and knee OA symptoms, limiting comparisons with the present findings and underscoring the need for future research that explicitly considers race.

As health care practices in the United States shift toward precision and targeted medicine, considering demographic factors that potentially influence mechanistic processes is imperative [13]. We acknowledge that our pilot investigation may not have immediate clinical implications. However, our race-specific findings may inform health care providers that treatments chiefly developed based on data from non-Hispanic Whites may not provide optimal analgesic care for Asian

Americans and suggest that the future development of novel OA treatment approaches may ultimately vary according to race, depending on the therapeutic target.

Based on our findings, future studies involving larger samples are required to validate our results and facilitate more advanced modeling (eg, with mediators/moderators) to augment current knowledge. In addition, future studies may substantially benefit from leveraging a larger pool of biomarkers that could be analyzed as possible correlational factors for knee OA symptoms. Simultaneously, several studies [5,39], including our own, have relied on a single marker as a measure of inflammatory status; however, recognizing that the inflammatory system is complex and involves multiple feedback mechanisms is indispensable. For example, a study by Zhu et al [38] attempted to address these issues by examining the patterns of 19 different inflammatory markers and adipokines derived from principal component analysis and subsequently exploring their association with knee OA symptoms. Future studies should ascertain whether these associations differ across racial/ethnic groups and also include individuals from other racial/ethnic minority groups, such as non-Hispanic Blacks and Hispanics.

Limitations

This pilot study has certain limitations. First, as this study represents a secondary, cross-sectional analysis of baseline data from a parent RCT, both the study design and the measures available for analysis were determined by the objectives of the parent trial rather than the specific aims of the current study. In addition, the sample size was defined by the feasibility-oriented goals of the parent pilot trial, rather than by statistical power considerations for the present secondary analysis. As such, the findings should be interpreted as exploratory. These design features may also introduce potential sources of bias, including selection bias related to the original eligibility criteria and measurement bias due to reliance on pre-specified baseline assessments. Second, the findings may not be generalizable as they are based on an extremely small convenience sample from a specific region. Furthermore, owing to the small sample size, we could not account for or control heterogeneity within racial groups (ethnicity). Third, the presence of unknown or unmeasured confounding factors, such as the use of nonsteroidal anti-inflammatory drugs, comorbid conditions, psychosocial factors like depression or anxiety, and synovial inflammation, cannot be ruled out. Fourth, the cross-sectional design hindered our ability to determine the directionality of the relationships between variables. Finally, our study was limited by the number of biomarkers assayed.

Conclusions

This pilot study provides pioneering evidence of race-specific relationships between inflammatory markers and knee OA symptoms among non-Hispanic Whites and Asian Americans. Based on our findings, racial/ethnic differences in this context warrant further exploration, with potential implications for the formulation of personalized strategies for managing knee OA symptoms.

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Data Availability

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

Authors' Contributions

CL and CKK were responsible for the conception or design of the work. HA contributed to the acquisition of the data. CL and CKK were involved in the analysis and interpretation of the data, as well as drafting the work. CKK and HA revised the manuscript critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Conflicts of Interest

HA is the Editor-in-Chief of *Asian/Pacific Island Nursing*. CKK reports consulting relationships with TLC, AposHealth, Kolon Tissue Gene, Express Scripts, Levicept, Enlivex, Pleryon, Avalor, GSK, Moebius Sun, Xalud, and Novartis. CNW's institution has received research grants from Amgen, Cumberland Pharmaceuticals, Novartis, Lilly, AbbVie, UCB, Pfizer, Artiva, and Bristol Myers Squibb.

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Abbreviations

CRP: C-reactive protein

IL-10: interleukin-10

KL: Kellgren–Lawrence

OA: osteoarthritis

PANAS: Positive and Negative Affect Schedule

PCS: Pain Catastrophizing Scale

SE: standard error

TNF- α : tumor necrosis factor-alpha

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Association Between Parental Smoking Status and Adolescent Mental Health: Population-Based Study

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Abstract

Background: Adolescents' mental health problems significantly affect their long-term psychological and physical health. Although peer influence grows during adolescence, parental influence remains critical. Parental smoking is associated with behavioral problems in adolescents.

Objective: This study aimed to investigate the association between parental smoking, particularly maternal smoking, and adolescents' mental health outcomes in South Korea, as research in this area is limited.

Methods: We analyzed data from the nationwide Korea National Health and Nutrition Examination Survey from 2012 to 2017. A total of 2761 adolescents were included in the final analysis after excluding those with missing data. We used ANOVA and chi-square tests to compare adolescents' and parents' baseline characteristics and mental health. In addition, multiple logistic regression analyses were conducted to examine the association between parental smoking status and adolescents' mental health.

Results: Our logistic regression analyses revealed that mothers' current smoking habits were significantly associated with their adolescents' cognitive stress (odds ratio [OR] 1.65, 95% CI 1.06 - 2.56), experiences of melancholy (OR 2.09, 95% CI 1.20 - 3.65), and suicidal ideation (OR 2.39, 95% CI 1.17 - 4.88). Furthermore, adolescents whose mothers were current smokers and had cognitive stress demonstrated higher cognitive stress (OR 2.09, 95% CI 1.12 - 3.90), melancholy (OR 2.27, 95% CI 1.10 - 4.71), and suicidal ideation (OR 2.74, 95% CI 1.21 - 6.23) than those whose mothers were not smokers and had no cognitive stress.

Conclusions: Efforts to improve adolescents' mental health require considering their mothers' smoking status and stress levels. This highlights the need to develop programs to enhance adolescent mental health, manage maternal stress, and promote smoking cessation.

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KEYWORDS

parental smoking; adolescent mental health; suicidal ideation; melancholy; cognitive stress

Introduction

Adolescence is a critical period for the development and maintenance of social and emotional habits that are important for mental health [1]. Mental health issues during adolescence have considerable long-term impacts on one's physical and psychological status, with parental behaviors playing a critical role in this developmental stage [2], including in school connectedness [3,4], emotional and physical health [5], substance misuse [6], and suicide-related injury risk [7,8]. Therefore, prevention and early intervention are essential for effective mental health management and improved social outcomes [9].

Several variables affect the mental health of children and adolescents, including school-, peer-, and family-related factors [10]. However, there is renewed interest in family-related factors

that affect children's mental health. In particular, the relationship between parental and children's mental health requires further verification and support [11].

Researchers have identified several parental health-risk behaviors as predictors of poor mental health in children. Parental smoking, particularly maternal smoking, is associated with internalizing and externalizing behavioral problems in children [12-14]. Maternal smoking has been linked to mental health issues in children, including symptoms of melancholy, anxiety, and suicidal ideation [15]. Parental smoking is associated with the initiation and regular use of smoking among children and adolescents [16]. The direct effects of smoking on children and adolescents may be attributed to an induced biological vulnerability to the addictive properties of nicotine, whereas the indirect effects may be driven by nicotine-induced behavioral problems in childhood [17].

A systematic review and meta-analysis showed that compared with smoking cessation, continued smoking was associated with increased depression, stress, and poor overall mental health [18]. However, to our knowledge, no studies have examined the association between parental smoking (as reported by parents) and adolescents’ mental health in Asian cultures. Furthermore, as Asian cultures are more receptive to men engaging in smoking than women, societal acceptance of female smoking remains low despite increasing smoking rates in women [19]. In South Korea, the prevalence of depression among adolescents reached 20.3% in 2021, and smoking remains a significant public health concern, with 4.5% of high school students reporting current use [20]. These high rates of mental health issues and smoking highlight the urgent need to understand the family-related factors influencing adolescent well-being in this cultural context.

We expected that parents’ sex and smoking status would have differential effects on the mental health outcomes of adolescents. This study examined the association between parental smoking, with a particular focus on maternal smoking, and adolescent mental health in the South Korean cultural context. The current

findings will contribute to a more nuanced understanding of these relationships.

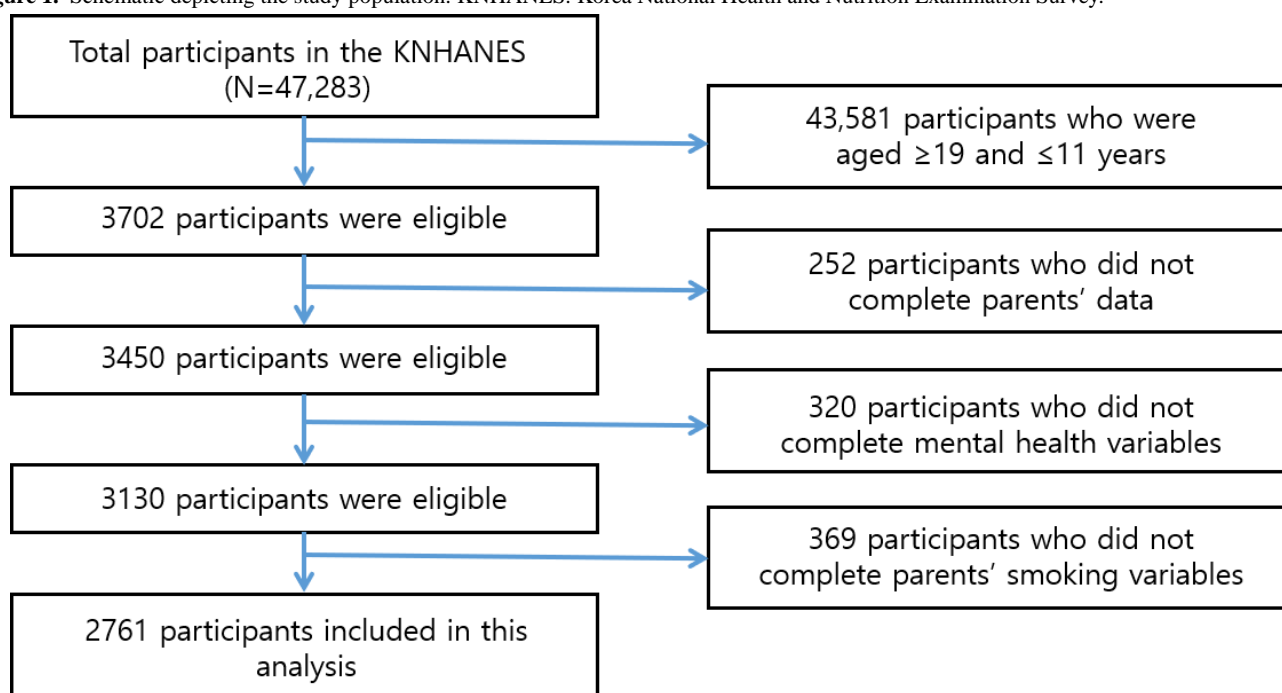
Methods

Study Design and Population

This study analyzed data from the Korea National Health and Nutrition Examination Survey (KNHANES), a cross-sectional, nationally representative survey conducted by the Korea Centers for Disease Control and Prevention from 2012 to 2017. The survey used a stratified multistage probability sampling design to draw a sample representative of the entire South Korean population. The KNHANES included health interviews, health behavior surveys, nutrition surveys, and health examinations.

Of the 47,283 participants enrolled in the KNHANES between 2012 and 2017, we included those aged 12 - 18 years (n=3702). Participants with missing parental (n=252), mental health (n=320), or parental smoking (n=369) variables were excluded. Finally, we examined the data of 2761 adolescents enrolled in the KNHANES (Figure 1).

Figure 1. Schematic depicting the study population. KNHANES: Korea National Health and Nutrition Examination Survey.



Research Variables

Baseline Characteristics

We recorded the following baseline characteristics of adolescents: age, sex, household and personal income levels, smoking status, and alcohol consumption. In addition, we recorded the following baseline parental characteristics: age, education level, current economic activity, BMI, waist circumference, smoking status, and alcohol consumption.

We classified household and personal income based on equivalent income,

average monthly household incomenumber of family members,

designating values reflecting the lowest 25% as the first quartile, and the subsequent 3 levels (25% each) as the second, third, and fourth quartiles. We categorized parental education levels as “below university graduation” and “university graduate or higher.” We organized current economic activity as “yes” or “no” to represent whether parents were currently employed or unemployed. We classified smoking status according to whether participants currently smoked. We considered participants who consumed more than 30 mL of alcohol per day as heavy drinkers.

Well-trained examiners performed anthropometric measurements during the study period. We acquired measurements for height and waist circumference to the nearest

0.1 cm using a portable stadiometer (Seca 225, Seca) and a calibrated ruler (Seca 200, Seca) after exhalation and from the narrowest point between the lower borders of the ribcage and the iliac crest. We measured weight to the nearest 0.1 kg using a calibrated balance-beam scale (GL-6000 - 20; G-tech). All instruments were calibrated regularly to ensure measurement accuracy, and inter-rater reliability tests were conducted periodically to minimize measurement bias. We calculated BMI as weight divided by height squared (kg/m^2).

Smoking Status

Smoking status was assessed using the question, "Are you currently smoking?" Participants could respond with "I smoke every day," "I smoke sometimes," "I smoked in the past, but I don't smoke currently," or "not applicable." We classified participants' smoking status as "current smoker," "ex-smoker," or "never smoked," with "current smoker" including "every day or occasional smoking."

Mental Health

The mental health variables included cognitive stress, experiences of melancholy, and suicidal ideation. The following questions were developed and reviewed by a panel of experts for epidemiological research, ensuring their validity as single-item questions. For cognitive stress, we classified the responses of "I feel very stressed," "I feel stressed a lot," and "I feel a little stressed" as "yes" and the response of "I hardly feel stressed" as "no." We determined whether participants experienced melancholy based on the question, "Have you felt sad or depressed for at least 2 consecutive weeks within the last year to the extent that it disturbed your daily life?" To this, participants could answer "yes" or "no." We assessed suicidal ideation using the question, "Have you thought of committing suicide in the last year?" The possible responses included "yes" and "no."

We did not measure "experiences of melancholy" as a parental mental health variable in this study; however, we measured the difference in adolescents' mental health based on whether their parents were diagnosed with depression. We defined participants

as being diagnosed with depression if they responded "yes" to the question, "Have you ever been diagnosed with depression by a doctor?"

Statistical Analysis

We used the SAS survey procedure (version 9.3; SAS Institute Inc) to run a complex sample design and analyze the survey data. Mean and SE values were used to represent continuous variables, and mean percentage and SE values were used to represent categorical variables. We used an ANOVA and the chi-square test to compare the baseline characteristics and mental health variables of adolescents and parents. Subsequently, we performed multiple logistic regression analyses to evaluate the association between adolescents' mental health variables and differences in parental smoking status. We examined the odds ratios (ORs) and 95% CIs after adjusting for age, sex, smoking status, alcohol consumption, and household income. In addition, we examined the ORs and 95% CIs in the association between adolescents' mental health and mothers' current smoking status and cognitive stress.

Ethical Considerations

The original data for the KNHANES were collected after being approved by the institutional review board of the Korea Centers for Disease Control and Prevention. Written informed consent was obtained from all participants prior to the original data collection. As this study is a secondary analysis using publicly available and deidentified data, it was determined to be exempt from a separate institutional review board review (number 1041078-202106-HRSB-172-01). No compensation was provided to participants for this specific analysis.

Results

Adolescents' Mental Health According to Adolescents' and Parents' Baseline Characteristics

Table 1 shows adolescents' mental health according to their baseline characteristics and mental health variables, along with those of their parents.

Table . Adolescents' mental health according to adolescents' and their parents' baseline characteristics (N=2761).

Variables	Cognitive stress			Experience of melancholy			Suicidal ideation		
	No (n=2059)	Yes (n=702)	P value	No (n=2536)	Yes (n=225)	P value	No (n=2600)	Yes (n=161)	P value
Adolescents									
Age (years), mean (SE) ^a	15.1 (0.05)	15.31 (0.08)	.02	15.12 (0.04)	15.52 (0.14)	.007	15.15 (0.04)	15.1 (0.16)	.73
Sex (male), mean % (SE) ^b	54.28 (1.19)	47.32 (2.10)	.005	53.78 (1.07)	38.69 (3.85)	<.001	53.47 (1.06)	37.24 (4.51)	<.001
Household income (lowest Q1), mean % (SE)	9.27 (0.95)	10.76 (1.40)	.34	9.43 (0.85)	12.03 (2.52)	.27	9.32 (0.81)	14.89 (4.01)	.09
Current smoker (yes), mean % (SE)	13.55 (0.90)	21.70 (1.91)	<.001	14.83 (0.86)	24.31 (3.35)	.001	14.98 (0.85)	25.84 (4.41)	.003
Heavy drinker (yes), mean % (SE)	31.93 (1.28)	41.48 (2.19)	<.001	32.61 (1.18)	53.36 (4.19)	<.001	33.38 (1.17)	49.83 (4.28)	<.001
Mothers									
Age (years), mean (SE)	44.15 (0.13)	44.62 (0.19)	.03	44.25 (0.12)	44.48 (0.35)	.52	44.26 (0.11)	44.41 (0.47)	.75
Education (≥ university), mean % (SE)	39.53 (1.55)	38.81 (2.32)	.77	39.62 (1.47)	36.32 (3.64)	.39	40 (1.44)	29.27 (4.10)	.02
Current economic activity (yes), mean % (SE)	66 (1.47)	63.2 (2.25)	.26	65.79 (1.34)	59.68 (3.99)	.12	65.29 (1.33)	65.15 (4.68)	.98
BMI (kg/m ²), mean (SE)	23.24 (0.09)	23.54 (0.17)	.10	23.29 (0.09)	23.58 (0.3)	.35	23.3 (0.09)	23.61 (0.38)	.42
Waist circumference (cm), mean (SE)	77.2 (0.25)	77.99 (0.46)	.11	77.36 (0.24)	77.81 (0.76)	.56	77.38 (0.24)	77.66 (0.94)	.77
Current smoker (yes), mean % (SE)	4.19 (0.61)	7.5 (1.24)	.006	4.66 (0.57)	9.16 (2.20)	.009	4.69 (0.56)	10.32 (3.24)	.02
Heavy drinker (yes), mean % (SE)	5.69 (0.71)	6.91 (1.27)	.36	5.71 (0.66)	9.24 (2.42)	.09	5.88 (0.66)	7.93 (2.65)	.39
Cognitive stress (yes), mean % (SE)	25.34 (1.41)	33.95 (2.16)	.001	26.42 (1.22)	39.78 (3.59)	<.001	26.69 (1.18)	40.64 (4.80)	.002

Variables	Cognitive stress			Experience of melancholy			Suicidal ideation		
	No (n=2059)	Yes (n=702)	P value	No (n=2536)	Yes (n=225)	P value	No (n=2600)	Yes (n=161)	P value
Diagnosis of depression (yes), mean % (SE)	3.89 (0.52)	5.21 (0.93)	.16	4.07 (0.48)	5.94 (1.79)	.23	4.1 (0.48)	6.25 (2.30)	.27
Fathers									
Age (years), mean (SE)	47.01 (0.15)	47.54 (0.23)	.04	47.11 (0.14)	47.41 (0.42)	.49	47.16 (0.14)	46.82 (0.53)	.54
Education (\geq university), mean % (SE)	50.72 (1.89)	45.87 (2.90)	.10	49.87 (1.81)	45.76 (4.69)	.38	49.89 (1.78)	43.87 (5.69)	.29
Current economic activity (yes), mean % (SE)	94.51 (0.88)	95.07 (1.15)	.66	94.67 (0.83)	94.39 (1.76)	.88	94.88 (0.77)	90.93 (4.25)	.24
BMI (kg/m^2), mean (SE)	24.89 (0.11)	24.70 (0.16)	.28	24.84 (0.10)	24.88 (0.26)	.90	24.84 (0.10)	24.99 (0.35)	.67
Waist circumference (cm), mean (SE)	86.12 (0.28)	86.19 (0.45)	.88	86.13 (0.27)	86.26 (0.65)	.84	86.09 (0.26)	86.85 (0.97)	.45
Current smoker (yes), mean % (SE)	42.95 (1.69)	46.15 (2.79)	.30	43.93 (1.59)	41.35 (4.40)	.58	44.11 (1.53)	37.34 (5.62)	.24
Heavy drinker (yes), mean % (SE)	25.46 (1.42)	28.86 (2.37)	.17	26.16 (1.36)	27.68 (4.01)	.71	26.78 (1.34)	18.17 (3.77)	.046
Cognitive stress (yes), mean % (SE)	29.03 (1.56)	32 (2.48)	.27	29.90 (1.44)	28.03 (3.87)	.65	29.6 (1.43)	32.3 (5.15)	.60
Diagnosis of depression (yes), mean % (SE)	2.07 (0.50)	0.42 (0.30)	.01	1.65 (0.41)	1.92 (1.15)	.81	1.73 (0.42)	0.68 (0.68)	.34

^aMean (SE) values represent continuous variables.

^bMean percentage (SE) values represent categorical variables.

Table . Adolescents’ mental health and maternal smoking status (N=2761).

Maternal smoking status	Cognitive stress			Experience of melancholy			Suicidal ideation		
	Mean % (SE)	Model 1 ^a , OR ^b (95% CI)	Model 2 ^c , OR (95% CI)	Mean % (SE)	Model 1 ^a , OR (95% CI)	Model 2 ^c , OR (95% CI)	% Mean (SE)	Model 1 ^a , OR (95% CI)	Model 2 ^c , OR (95% CI)
Never smoked	24.33 (1)	1 (ref ^d)	1 (ref)	7.82 (0.63)	1 (ref)	1 (ref)	5.53 (0.53)	1 (ref)	1 (ref)
Ex-smoker	35.19 (5.17)	1.72 (1.08-2.75)	1.63 (1.04-2.59)	10.52 (3.07)	1.45 (0.74-2.85)	1.32 (0.68-2.55)	10.23 (3.20)	1.97 (0.93-4.18)	1.74 (0.80-3.78)
Current smoker	37.83 (5.19)	1.88 (1.20-2.95)	1.65 (1.06-2.56)	15.07 (3.71)	2.09 (1.20-3.65)	1.64 (0.93-2.89)	12.39 (3.84)	2.39 (1.17-4.88)	1.72 (0.88-3.38)

^aModel 1: adjusted for adolescents’ age and sex.

^bOR: odds ratio.

^cModel 2: adjusted for adolescents’ age, sex, household income, current smoking status, and heavy drinking status.

^dref: reference.

Regarding adolescents’ cognitive stress, we found significant differences according to their age ($P=.02$), sex ($P=.005$), current smoking status ($P<.001$), and heavy drinking status ($P<.001$); maternal age ($P=.03$), current smoking status ($P=.006$), and cognitive stress ($P=.001$); and paternal age ($P=.04$) and diagnosis of depression ($P=.01$).

For adolescents’ experiences of melancholy, we observed significant differences according to their age ($P=.007$), sex ($P<.001$), current smoking status ($P=.001$), and heavy drinking status ($P<.001$), as well as maternal current smoking status ($P=.009$) and cognitive stress ($P<.001$). No significant associations were found for the paternal variables.

Suicidal ideation showed significant differences according to adolescents’ sex ($P<.001$), current smoking status ($P=.003$), and heavy drinking status ($P<.001$); maternal education level ($P=.02$), current smoking status ($P=.02$), and cognitive stress ($P=.002$); and paternal heavy drinking status ($P=.046$).

Association Between Adolescents’ Mental Health and Parental Smoking Status

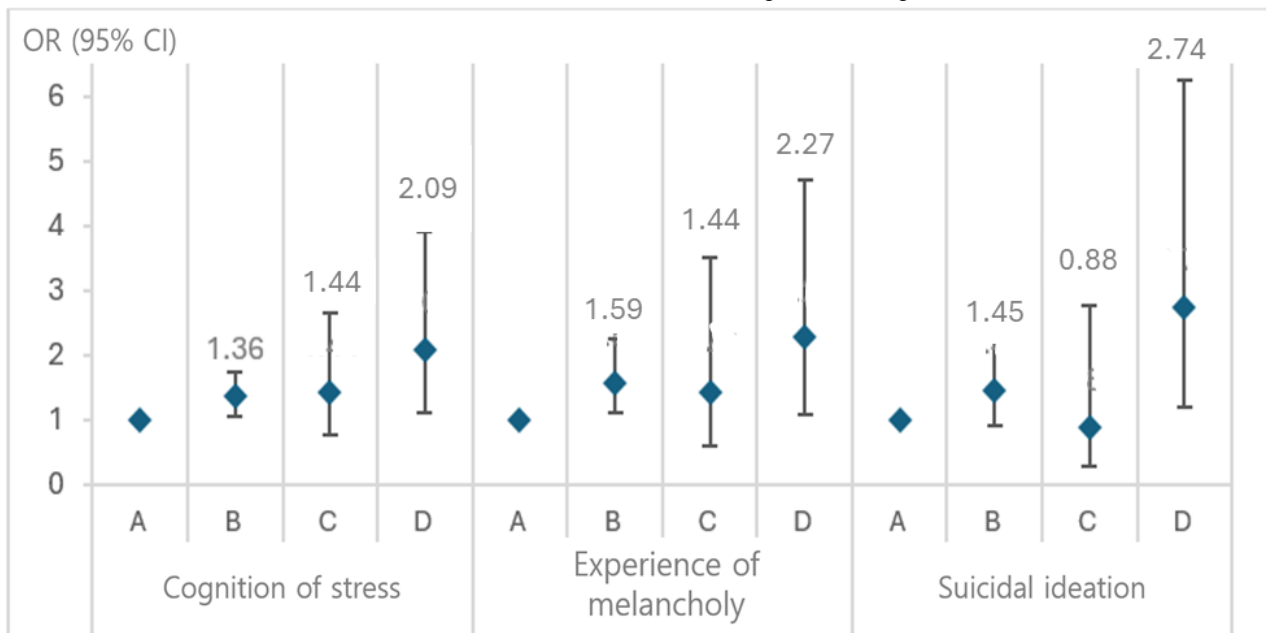
Table 2 presents the association between adolescents’ mental health and maternal smoking status. In Model 1 of the logistic regression analysis, we adjusted for adolescent age and sex. In Model 2, we adjusted for adolescent age, sex, smoking status, alcohol consumption, and household income. The analysis revealed that maternal smoking status was significantly associated with adolescents’ cognitive stress and melancholy ($P=.03$). The ORs for adolescents’ cognitive stress were 1.72 (95% CI 1.08 - 2.75) and 1.63 (95% CI 1.04 - 2.59) in Models 1 and 2, respectively, in the group with mothers who were ex-smokers; the ORs were 1.88 (95% CI 1.20 - 2.95) and 1.65

(95% CI 1.06 - 2.56) in Models 1 and 2, respectively, in the group with mothers who were current smokers. The OR for adolescents’ experience of melancholy was significant in Model 1 at 2.09 (95% CI 1.20 - 3.65) only in the group with mothers who were current smokers. In addition, the OR for adolescents’ suicidal ideation was significant in Model 1 at 2.39 (95% CI 1.17 - 4.88) only in the group with mothers who were current smokers. Paternal smoking was not significantly associated with adolescents’ mental health.

Association Between Adolescents’ Mental Health and Mothers’ Current Smoking Status and Cognitive Stress

Figure 2 shows the association between adolescents’ mental health and mothers’ current smoking status and cognitive stress. We classified mothers into 4 groups depending on their current smoking status and cognitive stress: Group A (reference group) for mothers who were “not current smokers and without cognitive stress,” Group B for mothers who were “not current smokers but with cognitive stress,” Group C for mothers who were “current smokers but without cognitive stress,” and Group D for mothers who were “current smokers with cognitive stress.” The significant ORs were 1.36 (95% CI 1.06 - 1.75) in Group B and 2.09 (95% CI 1.12 - 3.90) in Group D for adolescents’ cognitive stress, and 1.59 (95% CI 1.11 - 2.27) in Group B and 2.27 (95% CI 1.10 - 4.71) in Group D for adolescents’ experiences of melancholy.

However, adolescents’ suicidal ideation was significant for only Group D (OR 2.74, 95% CI 1.21 - 6.23). Figure 2 shows that adolescents’ mental health ORs in Group D (current smokers with cognitive stress) were higher than those in Group A (reference group).

Figure 2. Association between adolescents' mental health and mothers' current smoking status and cognitive stress (N=2761). OR: odds ratio.

Discussion

Principal Findings

This study examined the association between parental smoking status and the mental health of their adolescents in South Korea, specifically focusing on cognitive stress, melancholy, and suicidal ideation. Furthermore, we analyzed these factors separately for mothers and fathers to identify any differences in the effects.

We observed a significant relationship between adolescents' cognitive stress and their parents' age and current smoking status. As parents age and their physical aging progresses, their employment stability may decrease; in addition, they often have to care for their own older parents. This can expose their children to various stressful situations [21]. In addition, mental health problems such as parental depression can negatively affect children's cognitive health. However, strengthening protective factors across various areas of adolescents' lives may help prevent psychological health problems among adolescents [22]. Therefore, researchers should use multiple approaches to improve parental mental health and reduce perceived stress among adolescents.

Mothers' current smoking status and cognitive stress influenced their adolescents' experiences of melancholy, whereas fathers' smoking status had no such significant effect. Parent-child communication is related to adolescents' life satisfaction, with their relationships with mothers having a particularly strong influence on girls [23]. In contrast, adolescent aggression and depressive symptoms were associated with increased mother-adolescent conflict [24]. In South Korean culture, the mother-child relationship is notably close [25], which may explain why mothers have a stronger influence on their adolescents' mental health than fathers. The observed effects of maternal smoking could also be influenced by prevailing social norms. In many Asian cultures, women who smoke may be perceived as violating traditional norms, leading to moral

judgments (eg, viewed as less respectable, lacking self-control, or not family-oriented). This social stigma can indirectly affect adolescents' mental health through social pressure, family reputation concerns, or community gossip.

Reiss et al [26] analyzed data from the German National Health Interview and Examination Survey for children and adolescents, revealing that children of parents with higher education levels had fewer mental health problems in response to stressful life situations than their peers. Moreover, Guerrero et al [27] reported that the children of parents with lower education levels required interventions to address their risk of developing mental health problems due to stressful situations. These results echo those of our study, as parents' level of education can create high expectations for their children to study or go to school. In addition, the expression of conflict can be attributed to differences in one's future goals.

Maternal smoking and cognitive stress consistently had significant effects on adolescents' mental health, as mothers' smoking status was associated with their adolescents' cognitive stress, melancholy, and suicidal ideation. Adolescents whose mothers were current smokers and experienced stress exhibited higher cognitive stress, melancholy, and suicidal ideation than those whose mothers did not smoke or experience stress. Amrock and Weitzman [28] analyzed data from the National Health Interview Surveys in the United States to examine the mental health of children aged 4 - 17 years and identified a negative effect of parental mental health and sex on adolescent mental health. However, our study found that only maternal cognitive stress significantly affected adolescents' cognitive stress, melancholy, and suicidal ideation. This could be because in South Korea, mothers are primarily responsible for raising their children; thus, their mental health may have a more significant influence on their children than that of their fathers. Moreover, in a study comparing mothers' child-rearing stress in the United States and South Korea, South Korean mothers showed substantially higher stress levels than did American mothers [29].

Lee et al [30] found that adolescents' mental health was significantly associated with maternal mental health and smoking status but not with paternal mental health. This difference may be because fathers often display cooperative and constructive problem-solving behaviors that adolescents tend to emulate. However, their focus on problem-solving may reduce emotional engagement, making interactions feel less supportive than the warmth typically provided by mothers [31]. Moreover, maternal depression can impair mother-child attachment and elevate maternal stress, leading to diminished nurturing behaviors. This creates a stressful home environment, potentially resulting in developmental challenges and emotional difficulties for adolescents [32]. Children may develop psychological symptoms as a result of receiving insufficient support during challenging moments, thereby necessitating the consideration of parental mental health [33]. By addressing parents' needs through family support programs, health professionals can improve the mental and behavioral health of adolescents as well as the happiness and nurturing nature of parents. Such family support programs can be a part of treatment and prevention [34].

Stress is a significant risk factor for smoking, as individuals often smoke to reduce stress [35]. In South Korea, the negative perception of women smoking likely means that the actual number of female smokers is substantially higher than the officially reported smoking rates [36]. Therefore, women may be more likely to smoke in personal spaces, such as their homes, than in public areas; therefore, children may be more likely to be exposed to their mothers' smoking.

Our findings provide valuable evidence supporting the influence of parental smoking on adolescents' mental health. However, this study has some limitations. First, our cross-sectional design limits causal interpretation. We analyzed data from the nationwide KNHANES; therefore, the results are associative rather than causative, restricting our ability to confirm causal relationships between parental smoking and adolescent mental

health outcomes. Second, this study focused exclusively on South Korean adolescents and parents; therefore, the results may not apply to populations in different cultural or social environments, and their generalizability may be limited. Finally, the accuracy of self-reported parental smoking status remains a potential issue. The cultural stigma surrounding women engaging in smoking in South Korea may lead to the underreporting of mothers' smoking behaviors. Future research should consider a wider range of variables and interaction effects to provide a more comprehensive analysis of the factors affecting adolescent mental health and strengthen the understanding of these relationships across cultural contexts. In addition, future studies should incorporate longitudinal data to better understand the causality of these variables.

Limitations and Recommendations

The cross-sectional design of our study limits the ability to establish causality, while the self-reported nature of data presents a risk of underreporting, especially for maternal smoking due to cultural stigma. We recommend that future research use longitudinal data to better understand the causal relationships between variables. In addition, we suggest incorporating diverse measurement methods and standardized mental health scales to overcome the limitations of single-item, self-reported data.

Conclusions

We examined the relationship between parental smoking status and the mental health of adolescents in South Korea and found a significant association between adolescents' mental health and mothers' current smoking status. Moreover, maternal stress has a substantial association with their adolescents' well-being. We recommend programs to support mothers in managing their stress without having to rely on smoking and to quit smoking, as this can lead to improvements in their children's mental health. Therefore, systematic support at the national and domestic levels is required. Future research should explore additional factors affecting both parents' and adolescents' mental health.

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Conflicts of Interest

None declared.

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Abbreviations

KNHANES: Korea National Health and Nutrition Examination Survey

OR: odds ratio

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Personal Agency Support Questionnaire in Acute Psychiatric Inpatients: Development and Instrument Validation Study

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Abstract

Background: Promoting personal agency may reduce perceived coercion and facilitate recovery in acute psychiatric care. However, no patient-reported tool currently exists to evaluate support for personal agency in this setting.

Objective: This study aimed to develop a patient-reported tool (the Personal Agency Support Questionnaire [PASQ]) to assess perceived support for personal agency and to evaluate its psychometric properties among inpatients in acute psychiatric wards.

Methods: We used a literature review and focus group interviews to generate a pool of items for the questionnaire, which was then refined using cognitive interviews and a pretest. We evaluated the construct validity, internal consistency, and test-retest reliability of the newly developed PASQ using a cross-sectional survey of inpatients in acute psychiatric wards. This study was conducted in collaboration with individuals who have lived experiences of mental illness.

Results: We analyzed data from 109 respondents (response rate: 109/178, 61.2%; mean age: 52.9, SD 16.9 years; women participants: 59/109, 54.1%; diagnosed with schizophrenia: 61/109, 56%). The 10-item PASQ demonstrated excellent convergent validity and acceptable discriminant validity. Internal consistency was high (Cronbach $\alpha=0.92$), and test-retest reliability was moderate (intraclass correlation coefficient 0.68).

Conclusions: This PASQ is a valuable tool for assessing personal agency support in acute psychiatric wards, demonstrating promise for both clinical use in acute psychiatric wards and clinical research.

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KEYWORDS

inpatients; mental disorders; mental health; personal autonomy; psychometrics; surveys and questionnaires

Introduction

Acute psychiatric wards provide rapid treatment to stabilize the symptoms of individuals whose acute mental health challenges cannot be fully managed by community services [1]. Because acute psychiatric symptoms temporarily influence cognitive processes and impair behavioral control [2,3], involuntary treatment and behavioral restrictions are sometimes used to ensure safety [4]. Although many inpatients experience therapeutic benefits from psychiatric hospitalization, it is often a negative experience, with previous studies indicating a high frequency of traumatic events [5,6] that affect patients' well-being and self-worth [7,8]. This increased distress caused by inpatient stays can lead to the subsequent avoidance of mental health services [6].

The psychiatric care system in Japan has one of the largest numbers of psychiatric beds globally (approximately 319,000),

and a long average length of stay (263.2 d) remains a persistent concern [9]. To address this issue, the government has been promoting a shift from long-term hospitalization to community-based care, making the role of acute psychiatric wards—which emphasize short-term stabilization of acute symptoms—increasingly important [10]. Almost half of patients occupying these beds are there involuntarily, and Japanese acute wards use restrictive treatments at significantly higher rates than other countries [11,12]. Key strategies for addressing this urgent issue include minimizing the use of restrictive practices and enhancing staff awareness of the importance of supporting patients' personal agency [5].

Personal agency is defined as an individual's ability to control their own lives, pursue their goals [13,14], and perceive a sense of ownership of their own behavior [15]. It incorporates concepts such as intentionality, forethought, self-reactivity, and self-reflectiveness and operates through cognitive, motivational,

affective, and choice processes [13]. Personal agency has been conceptualized as encompassing both intrinsic (internal states of being, such as self-confidence and self-awareness) and instrumental (ways of acting, such as goal-directed decision-making and behavioral control) agency [16,17]. This framework builds upon prior conceptualizations of agency, such as Kabeer's distinction between "power within" and "power to" [18].

Personal agency is conceptually related to other key concepts in psychiatric care, such as autonomy, empowerment, and personal recovery. Autonomy is commonly understood as acting in line with one's own values in psychiatry [19] and is regarded as an outcome achieved through processes that constitute personal agency [13,19,20]. In mental health services, support for autonomy emphasizes the promotion of self-determination, with shared decision-making highlighted as a contemporary approach [21,22]. Empowerment is a process by which individuals gain greater control over the decisions and actions that affect their health [23], encompassing both personal agency and broader social and environmental transformation [24]. Personal recovery refers to living a fulfilling life despite experiencing psychiatric symptoms [25] and represents a comprehensive framework in which personal agency is a central driving force that facilitates the recovery process [26-28]. In acute psychiatric care, symptoms and safety requirements often limit the extent to which higher-order processes, such as autonomy and empowerment, can be expressed [19,29]. In contrast, personal agency remains a central mechanism within the recovery process regardless of symptom severity or treatment phase [26-28,30]. Therefore, clarifying how personal agency is supported in daily care is particularly important in acute settings. Personal agency plays a crucial role in reducing feelings of coercion and involuntariness during hospitalization [8]; moreover, it contributes to patient engagement in care and long-term recovery [31,32].

Despite its importance, there are currently no tools available to assess support for personal agency from the patient's perspective. In acute settings, understanding how patients perceive the support they receive and how their voice is reflected in clinical practice is essential for maintaining a balance between safety and patients' personal agency and ultimately fostering care that supports their recovery. Therefore, the aim of this study was to develop and validate the Personal Agency Support Questionnaire (PASQ) as a practical checklist-type questionnaire, rather than a psychometric scale that measures latent constructs, that captures patient-perceived support for personal agency in acute psychiatric settings.

Methods

Overall Design

This study was conducted within acute psychiatric care settings, where supporting personal agency is especially relevant and challenging owing to acute symptoms, rapid clinical decision-making, and safety needs. It consisted of 3 phases. The development and psychometric evaluation of the PASQ were guided by the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) checklist, which

provides international standards for studies on measurement properties of health-related instruments (Checklist 1).

In phase 1, we conducted a literature review and focus group interviews to generate an item pool for the new questionnaire. Subsequently, we conducted cognitive interviews to refine these items.

In phase 2, we conducted a pretest to verify whether the questionnaire items were appropriate for the target group and evaluate the likely responses.

In phase 3, we evaluated the validity and reliability of the PASQ by a cross-sectional survey of inpatients in acute psychiatric wards. Reporting of phase 3 followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies [33] to ensure methodological rigor and transparent reporting (Checklist 1).

Phase 1: Developing an Initial Item Pool and Cognitive Interview

In phase 1, we conducted a literature review and focus group interviews guided by best-practice recommendations for item pool generation [34]. We referred to existing patient-reported scales assessing various factors, such as recovery, empowerment, and autonomy, that had demonstrated reliability and validity for evaluating individuals with mental illness. From these scales, we incorporated the perspectives of research collaborators with lived experience of mental illness and extracted items according to 3 criteria: (1) the support aligned with personal agency; (2) the support included only the direct experiences of patients' interactions with staff, rather than support provided by hospitals or services; (3) the support focused on foundational aspects of personal agency relevant to acute psychiatric care, rather than directly targeting long-term social participation or self-actualization.

Through team discussions, we grouped items that met these criteria according to similarity in meaning to reduce redundancy and organize the item pool.

In parallel, focus group interviews were conducted with individuals who had experienced acute psychiatric hospitalization within the past 10 years. Participants were recruited from welfare service centers and nonprofit organizations in the Kansai region of Japan using convenience sampling (this approach was used primarily because of existing collaborative networks and logistical feasibility). The focus group interviews aimed to identify support that contributed to personal agency during acute hospitalization. Data collection and analysis were conducted iteratively and concurrently to capture diverse narratives, including unspoken perspectives and differing patterns. For the analysis, we focused on the experiences that were commonly identified as support for personal agency across participants, taking into account differences in backgrounds and experiences. These experiences were integrated and organized according to similarity.

Based on these findings, semantically redundant items were removed or integrated. Through collaborative discussions with our research collaborators with lived experience of mental illness, we selected items that supported personal agency while

also considering the psychological burdens and contextual constraints of acute psychiatric settings. During this process, we examined how each support type was perceived and its effectiveness in acute contexts. For example, for the item of “information provision,” participants stated that “too much information can be confusing, and it is more important to understand what is happening now and what to do next.” Upon reflection of such views, the item was refined to ensure that it evaluated whether information was provided at a time and in a manner that patients could understand and accept.

Content validity was examined collaboratively alongside four research collaborators with lived experience of mental illness and one clinical expert. All reviewed each item for clarity, relevance to support for personal agency, and appropriateness for acute psychiatric contexts. A cognitive interview was then conducted with one of the focus groups to confirm that the instructions and item wording could easily be understood.

Phase 2: Pretest

In phase 2, we conducted a pretest with 20 people from 2 acute wards of a psychiatric hospital. One of these wards later participated in the main survey in phase 3 in May 2024. The pretest involved assessing the extent of the burden on questionnaire respondents and identifying items that were frequently left unanswered or often received identical responses.

Phase 3: Evaluation of the Questionnaire

Setting and Participants

To evaluate the validity and reliability of the PASQ, we conducted a cross-sectional survey among inpatients in 6 acute psychiatric wards across 2 psychiatric hospitals in Japan. The hospitals were selected using convenience sampling. Coincidentally, both hospitals were accredited by the Japan Council for Quality Health Care, which ensured a more structured and higher-quality treatment environment compared with many other psychiatric facilities in Japan.

Inpatients were included in this study if they met the following criteria: (1) they had been hospitalized for at least 1 week during their current stay; (2) the attending psychiatrist had confirmed that their mental state and treatment would not be affected by participation in the research; and (3) they were aged 18 years or older. We excluded inpatients who (1) were in isolation or physically restrained; (2) were primarily being treated for a physical illness; and (3) had a diagnosis of dementia or intellectual disability. Nursing managers in each ward identified eligible patients admitted during the study period (from May to September 2024). The first author explained the study to each participant and obtained their informed consent. The estimated required sample size for phase 3 was 100 participants, in accordance with the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) checklist [35], which provides international guidelines for measurement studies.

Data Collection Procedures

The first author distributed paper-based self-administered questionnaires to each participant. If requested, the first author read the questions aloud or completed responses on the

participants' behalf, using only the exact wording of the items without providing additional explanations to minimize response bias. Participants were informed that their responses would remain confidential, would not affect their treatment, and would never be disclosed to the hospital staff involved in their care. They could either return the questionnaire to the first author directly or seal it in an envelope and place it in the ward's collection box to ensure privacy.

Measures

The Personal Agency Support Questionnaire

The PASQ is a newly developed tool for assessing perceived support for personal agency even under restricted environments, including acute psychiatric care settings. It is rated on a 5-point Likert-type scale (0=“not at all” to 4=“very much”). A higher score indicates higher perception of the support for personal agency. As it assesses it in a checklist-like manner, it is not expected to be normally distributed. The Japanese version of the scale is provided in [Multimedia Appendix 1](#).

The Japanese Version of Brief INSPIRE (Brief INSPIRE-J)

Given that personal agency is considered a central mechanism supporting personal recovery, and recovery-oriented support is conceptually linked to personal agency, we used the Brief INSPIRE-J to assess convergent validity. It is a shortened, 5-item version of the INSPIRE measure. Each item corresponds to 1 aspect of the concept of personal recovery (connection, hope, identity, meaning and purpose, and empowerment) and is rated on a 5-point Likert-type scale (0=“not at all” to 4=“very much”) [36]. A higher score indicates greater satisfaction of the service user with the professional support they received in their recovery-oriented practice. The validity and reliability of Brief INSPIRE-J have been confirmed in Japan (Cronbach $\alpha \geq 0.82$) [37]. In this study, the Brief INSPIRE-J exhibited high internal consistency, with a Cronbach α of 0.92.

The Japanese Version of the Kessler 6-Item Psychological Distress Scale

Because the psychological distress scale assesses internal emotional states [38], while the PASQ measures the perception of support, these 2 scales are theoretically assumed to assess conceptually distinct constructs. Therefore, we used the Kessler 6-item Psychological Distress Scale (K6) to examine divergent validity. The K6 comprises 6 items that ask respondents how frequently they have experienced symptoms of psychological distress. It is rated on a 5-point Likert-type scale (0=none of the time to 4=all the time) [38], with higher scores indicating a greater likelihood of the respondent having experienced distress. The Japanese version demonstrated equivalent screening performance to that reported for the original English versions (the area under the receiver operating characteristic curve 0.94, 95% CI 0.88 - 0.99) [39]. For K6 in this study, Cronbach $\alpha=0.80$, indicating good internal consistency.

Statistical Analysis

First, we conducted a descriptive analysis to examine the distribution of responses. Convergent validity was assessed assuming a significant and positive correlation with Brief INSPIRE-J; divergent validity was examined assuming an

insignificant correlation with K6. The Shapiro-Wilk test demonstrated that the PASQ had a nonnormal distribution; therefore, Spearman's rank correlation coefficients, 95% CI, and *P* values were calculated. Correlation coefficients were interpreted based on Akoglu [40] as follows: 0.00 - 0.19: none/very weak; 0.20 - 0.39: weak; 0.40 - 0.59: moderate; 0.60 - 0.79: strong; and 0.80 - 1.00: very strong.

We calculated Cronbach α coefficients to measure internal consistency, with a value of 0.70 or higher considered sufficient [41]. We also calculated Cronbach α after removing each item and item-to-total correlations, which indicated how well each item aligned with the overall construct. In addition, to prevent inflation of the correlation value, we calculated corrected interitem correlations and the correlation between each item and the sum of the others. Item-to-total correlation and corrected interitem correlations of 0.30 or higher were considered acceptable [42], suggesting that the item contributed well to the overall reliability of the PASQ.

We assessed test-retest reliability in targeting 20 participants over approximately 2 weeks. This interval was established based on previous research, assuming that the memory and experience of the first response would not influence the second response and that little would change between responses. We calculated the intraclass correlation coefficients (ICCs) between the 2 time points to examine test-retest reliability. ICC values were classified as poor (<0.50), moderate (0.50 - 0.75), good (0.75 - 0.90), or excellent (>0.90), in line with Koo and Li [43]. Because the PASQ was developed as a short assessment questionnaire in a checklist manner, following previous studies [44,45], we did not perform factor analysis.

All statistical analyses were performed in *R* (Version 4.4.1; R Core Team) [46]. We used the psych [47] and tidyverse [48] packages for descriptive statistics and reliability analyses and the psych [47], lavaan [49], and irr [50] packages for ICCs. A *P* value of <.05 was considered statistically significant (2-tailed test).

Patient and Public Involvement

Because this research focused on patients' subjective experiences, 4 individuals who had experienced acute psychiatric admissions were involved as research collaborators throughout this study. They advised on the clarity and comprehensibility of item wording and the survey procedures to ensure that the items reflected patients' lived experiences during acute psychiatric hospitalization. Their feedback led to some of the items being revised to better reflect perceived support that is responsive to the individual's sense of readiness and current mental state. This patient and public involvement process followed ethical guidelines and adhered to the principles of meaningful involvement [51]. The study collaborators received a 5000 Japanese yen (US \$31.60) gift card as a token of appreciation for attending 2 or 3 meetings.

Ethical Considerations

Because this study involved acute psychiatric inpatients, certain considerations were applied to the recruitment of participants. Attending psychiatrists could restrict the first author from approaching patients to explain the study, if such contact could

negatively impact patients' treatment. The first author, who had no clinical or organizational role at the hospitals, explained the study to individual patients privately, without staff present. The voluntary nature of participation, the absence of any effect on treatment, and confidentiality were explained both verbally and in writing, and written informed consent was obtained from all patients. To ensure privacy, data were anonymized in a linkable manner to allow for consent withdrawal. Personal identifiers were stored separately. Data were managed on a password-protected computer and in a locked cabinet. No compensation was provided to participants. The study was approved by the Ethics Committee of the Kobe University Graduate School of Health Sciences and the Graduate School of Medicine at Kyoto University (approval 1172 and R4367), as well as the Ethics Committee of the participating hospital (approval 2024 - 1).

Results

Phase 1: Developing an Initial Item Pool and Cognitive Interview

From the 330 items extracted from existing patient-reported measures, 94 items were selected according to item-selection criteria and grouped according to similarities (eg, respect for strengths and values, support for coping with difficulties, and assistance with decision-making). Focus group interviews were conducted with 12 individuals. Over 8 sessions, commonly reported experiences of support for personal agency in acute settings were identified, such as feeling safe, the ability to express thoughts openly, and the ability to make choices based on recovery level. By integrating insights from both the literature review and the focus group interviews, 10 items were selected, and consensus was reached among the researchers and research collaborators on all items, including their wording and clarity. The cognitive interview confirmed that all items could be easily understood by patients. The instructional texts were revised to ask respondents to reflect on the support received throughout their entire hospitalization and to rate support provided by all staff members in the ward rather than specific individuals.

Phase 2: Pretest

The pretest was conducted with 21 participants from 2 wards. Although 4 participants required assistance (eg, reading support), all completed the questionnaire within approximately 5 minutes. No missing data or extreme response biases were observed.

Phase 3: Evaluation of the Questionnaire

Study Participants

During the recruitment period, we explained the study to 113 of 178 eligible inpatients. Four participants did not return their questionnaires, but the remaining 109 (response rate 61.2%) provided responses and were included in the analysis. Of these 109 participants, 14 (12.8%) requested assistance with either reading the questions or writing their answers. There were no missing values for the main variables. Participant characteristics are presented in Table 1. Over half of the participants (59/109, 54.1%) were women. The overall mean age of participants was 52.9 (SD 16.9) years. Schizophrenia was the most common

diagnosis (62/109, 56%), followed by mood disorders (32/109, 29.4%).

Table . Demographic and clinical characteristics of respondents^a.

Variables	Values (N=109)
Age (y), mean (SD)	52.9 (16.9)
Duration of illness (y), mean (SD)	18.9 (15.9)
Length of current hospitalization (d), mean (SD)	36.4 (30.9)
Gender, n (%)	
Women	59 (54.1)
Men	50 (45.9)
Diagnosis, n (%)	
Schizophrenia	61 (56.0)
Mood disorders	32 (29.4)
Substance abuse	7 (6.4)
Anxiety disorder	4 (3.7)
Developmental disability	4 (3.7)
Epileptic psychosis	1 (0.9)
Type of hospitalization at the time of admission, n (%)	
Involuntary hospitalization for medical protection	66 (60.6)
Voluntary hospitalization	34 (31.2)
Involuntary hospitalization	7 (6.4)
Emergency hospitalization	2 (1.8)
Type of hospitalization at the time of the survey, n (%)	
Involuntary hospitalization for medical protection	56 (51.4)
Voluntary hospitalization	49 (45.0)
Involuntary hospitalization	4 (3.7)
Number of previous admissions to a psychiatric hospital, n (%)	
None	24 (22.9)
One	10 (9.5)
Two or more	71 (67.6)

^aSubsample sizes vary for some variables because of missing responses (n=107 for age, n=105 for number of previous admissions to a psychiatric hospital, and n=99 for duration of illness).

Distribution of the Responses

Table 2 and Figure 1 illustrate the distribution of the responses to each item of the PASQ. Responses were generally skewed toward the higher categories (“quite a bit” and “very much”), with a median score of 3 for all items. Mean scores ranged from 2.48 (SD 1.29) to 2.93 (SD 1.21). A high proportion of respondents (almost 70%) answered “quite a bit” or “very much” to the following items: “Medical staff respect me as a person (75/109, 68.8%),” “Medical staff are involved so that I have a

feeling of safety (77/109, 70.6%),” and “Medical staff provide support so that I can handle trouble (76/109, 69.7%).” Although these 3 items and item 6 demonstrated ceiling effects, they were retained to maintain content validity. In contrast, less than 60% of participants answered “quite a bit” or “very much” to the following items: “Medical staff try to understand the reason for my actions (63/109, 57.8%),” “Treatment and care are in line with what I want and the way I wish to be (63/109, 57.8%),” and “Medical staff share future treatment plans and expectations with me (62/109, 56.9%).”

Table . Personal Agency Support Questionnaire item responses and item-to-total correlations (N=109).

Item ^a	Mean (SD)	Median (IQR ^b ; range)	Cronbach α when item is deleted ^c	Item-to-total correlation ^d	Corrected Interitem correlation ^e
1	2.83 (1.21)	3 (2; 0-4)	0.92	0.65	0.57
2	2.76 (1.18)	3 (2; 0-4)	0.91	0.78	0.72
3	2.93 (1.21)	3 (2; 0-4)	0.91	0.71	0.64
4	2.84 (1.16)	3 (2; 0-4)	0.91	0.81	0.76
5	2.61 (1.25)	3 (2; 0-4)	0.92	0.63	0.54
6	2.70 (1.32)	3 (2; 0-4)	0.91	0.75	0.67
7	2.48 (1.29)	3 (1; 0-4)	0.91	0.79	0.73
8	2.62 (1.35)	3 (2; 0-4)	0.91	0.80	0.74
9	2.51 (1.41)	3 (2; 0-4)	0.91	0.81	0.75
10	2.67 (1.31)	3 (2; 0-4)	0.90	0.84	0.79

^aThe wording of each item is presented in Figure 1.

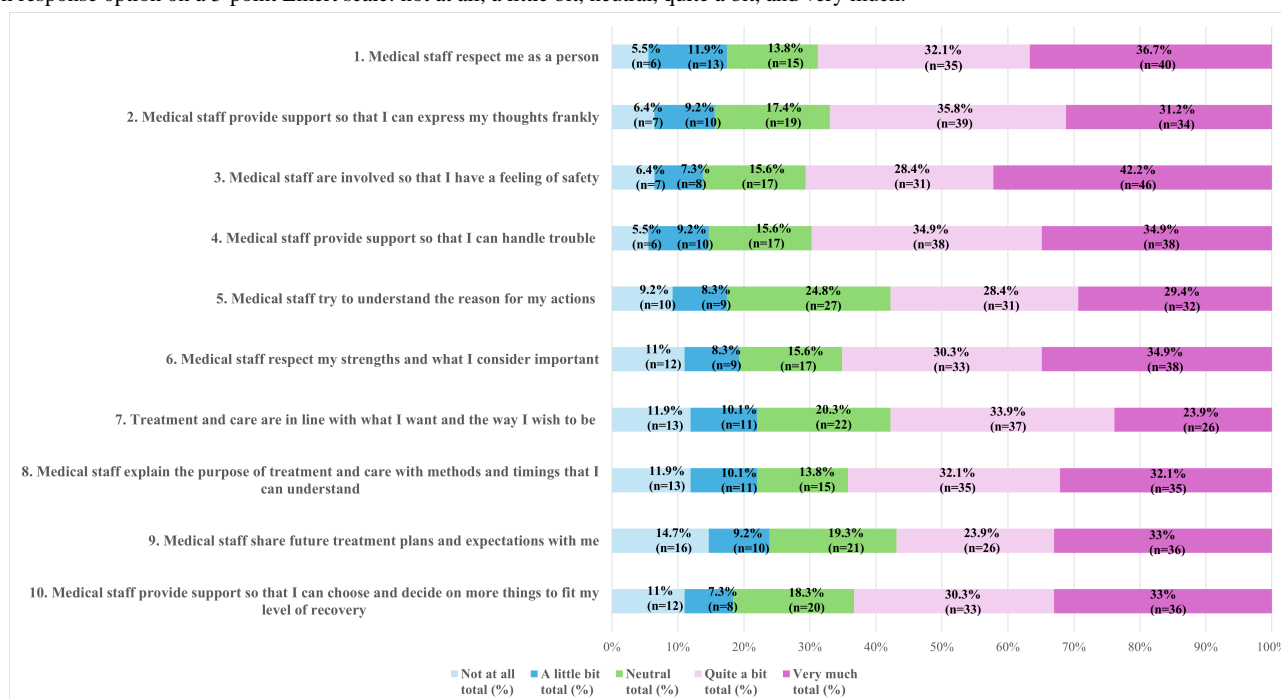
^bIQR: interquartile range.

^cCronbach α when item is deleted: reliability coefficient of the scale if the respective item is removed.

^dItem-to-total correlation: correlation between the item and the total scale score excluding that item.

^eCorrected interitem correlation: average correlation between the item and all other items.

Figure 1. Distribution of responses to the Personal Agency Support Questionnaire items (N=109). Bars represent the percentage of participants selecting each response option on a 5-point Likert scale: not at all, a little bit, neutral, quite a bit, and very much.



Convergent and Divergent Validity

We found significant positive correlations between the total PASQ and total Brief INSPiRE-J scores ($\rho=0.75$, 95% CI 0.63 - 0.85; $P<.001$). There were significant weak and negative correlations between the total PASQ and total K6 scores ($\rho=-0.32$, 95% CI -0.49 to -0.13 ; $P<.001$).

Reliability

The total score of the PASQ demonstrated sufficient homogeneity of all items, with a Cronbach α coefficient of 0.92.

No single item substantially reduced the internal consistency, with Cronbach α coefficients ranging from 0.90 to 0.92 when each item was removed. Item-to-total correlations ranged from 0.63 to 0.84, indicating strong associations between each item and the overall scale, while corrected interitem correlations ranged from 0.54 to 0.79, suggesting adequate interitem relatedness without excessive redundancy. The ICC value for the total score was 0.68 (95% CI 0.37-0.86; $n=21$), indicating moderate test-retest reliability.

Discussion

Key Findings and Interpretation

The newly developed PASQ assesses patients' perceptions of the support for their personal agency. Although some participants required assistance to complete the survey, most were able to respond appropriately independently. This suggests that the PASQ is feasible for use in acute psychiatric wards. It also exhibited adequate convergent validity, acceptable divergent validity, good internal consistency, and moderate test-retest reliability among inpatients in acute psychiatric wards in Japan.

Although there are existing scales assessing support for similar concepts related to personal agency, such as empowerment and personal recovery [52-54], the PASQ is the first scale developed to evaluate support for personal agency. Several items generated from our study shared similarities with existing tools, such as the Health Care Climate Questionnaire, which assesses professionals' support for patients' autonomy [55]. Given that the Health Care Climate Questionnaire does not specifically assess care for patients with mental illness or acute care, the similarities observed between these tools suggest that there are fundamental elements involved in supporting patient personal agency, regardless of the type or stage of illness. However, each item of the PASQ reflects fundamental support elements in acute psychiatric wards. For example, the items related to a feeling of safety and respect reflect the importance of relational safety in acute psychiatric care, as highlighted in previous studies [56-58]. Support aligned with personal values, as captured by several items, contributes to self-understanding and a sense of consistency [59]. Furthermore, providing appropriate information and stage-appropriate choices, as addressed by other items, supports the regaining of control [8].

The relatively high scores for items related to a sense of safety and respect suggest that the psychiatric facilities prioritize these aspects during the acute phase of care. However, comparatively lower scores for items "Medical staff try to understand the reason for my actions," "Treatment and care are in line with what I want and the way I wish to be," and "Medical staff share future treatment plans and expectations with me" may reflect the challenge in supporting patients to participate in their treatment during the acute phase, despite its importance for personal agency [8,59,60].

PASQ and Brief INSPiRE-J scores exhibited a significant and strong correlation, confirming convergent validity. This finding supports the proposition that personal agency is key to promoting personal recovery [26-28]. The weak but significant negative correlation between PASQ and K6 did not support our hypothesis. However, this finding is consistent with previous studies, which found a negative relationship between personal agency and psychological distress [61,62]. It is therefore possible that perceived support for personal agency may be slightly associated with the extent of anxiety or depression, supporting the distinction between these concepts and the discriminant validity of the PASQ.

The PASQ exhibited high internal consistency, indicating sufficient homogeneity. Cronbach α values remained stable

when items were deleted, suggesting limited redundancy. Item-to-total correlations were moderate to high, confirming that each item contributed meaningfully to the total score and that item deletion was not warranted. However, the moderate test-retest reliability suggests that the PASQ may not be entirely stable over time. This could be attributed to the rapid fluctuations in patients' conditions in acute psychiatric settings [63] during the 2-week interval or the slightly smaller sample size in this study.

Limitations and Strengths

This study has 2 main limitations. First, it was conducted at only 2 psychiatric hospitals, both of which provide relatively high-quality care. This may explain the relatively high scores observed, suggesting that our findings may not be generalizable to a broader range of clinical settings. Differences in staffing levels, staff training and attitudes, collaboration with community services, and the physical environment may all affect how support for personal agency is provided and perceived. Future research should therefore examine the applicability and validity of the PASQ in more diverse psychiatric settings. Second, the test-retest reliability was not excellent, with wide 95% CIs, which may reflect changes in patient symptoms and the care context during the 2-week interval; a shorter interval with a larger sample size might be more appropriate for acute psychiatric settings. Despite these limitations, this study is valuable as the first to develop a questionnaire for assessing perceived support for personal agency in acute psychiatric wards. It is also strengthened by the involvement of individuals with lived experience of acute psychiatric hospitalization, who helped to ensure that the PASQ reflects users' perspectives in acute settings.

Implications for Nursing Practice

The PASQ offers a practical approach to enable medical staff to understand how patients perceive support for personal agency in acute psychiatric wards and to apply these perspectives to clinical practice. Nurses, who work most closely with patients, face the challenge of maintaining a balance between delivering treatment, ensuring safety, and supporting patients' agency [64]. The PASQ may be helpful for nurses to gain an understanding of patients' subjective experiences and guide individualized care. Future studies could explore the use of the PASQ in staff training, interprofessional education, collaborative care planning in acute settings, and routine clinical reflection to enhance therapeutic engagement and communication. Furthermore, although the PASQ was developed and validated in acute settings, it may also be relevant in other contexts where agency may be compromised, such as long-term psychiatric hospitalization or trauma-related experiences. Future research should explore its applicability in such settings.

Conclusion

In this study, we developed and validated the PASQ, a patient-reported questionnaire that assesses perceived support for personal agency in acute psychiatric inpatients. The questionnaire demonstrated adequate convergent validity, acceptable divergent validity, good internal consistency, and moderate test-retest reliability. The PASQ shows promise as a

valuable tool for both clinical practice in acute psychiatric wards and future clinical research.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: TK
Data curation: TK, MS
Formal analysis: TK
Funding acquisition: TK
Methodology: TK, RC, YH
Project administration: TK
Supervision: RC, YH, and MS
Writing – original draft: TK
Writing – review & editing: RC, YH, and MS

Conflicts of Interest

None declared.

Multimedia Appendix 1

Personal Agency Support Questionnaire (PASQ), Japanese version.

[PDF File, 335 KB - [apinj_v10i1e83366_app1.pdf](#)]

Checklist 1

STROBE and COSMIN checklists.

[PDF File, 421 KB - [apinj_v10i1e83366_app2.pdf](#)]

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Abbreviations

COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments

ICC: intraclass correlation coefficient

K6: Kessler 6-item Psychological Distress Scale

PASQ: Personal Agency Support Questionnaire

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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