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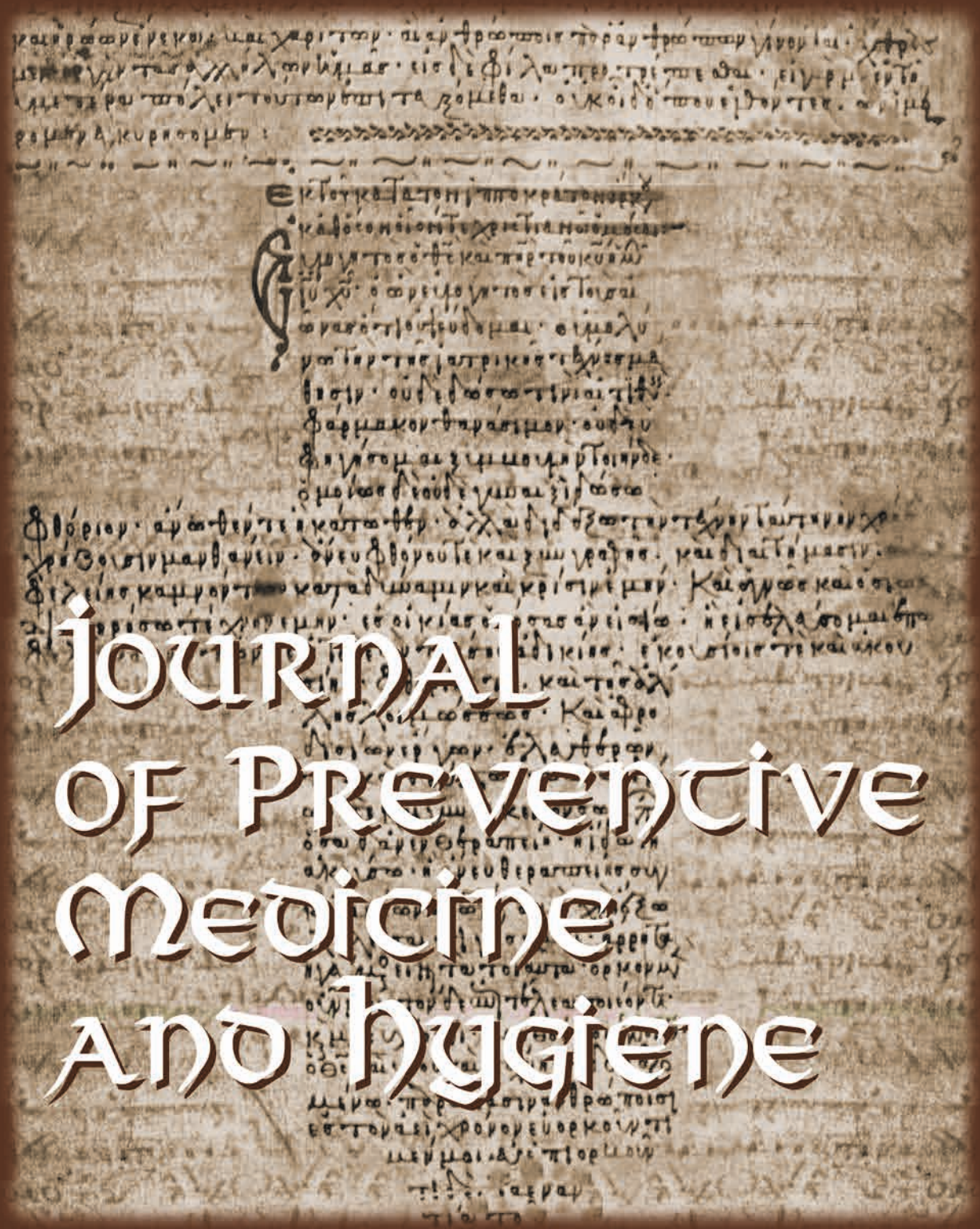

The original document of Hippocrates' oath

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Contents

HEALTH PROMOTION

The effects of social isolation and problematic social media use on well-being in a sample of young Italian gamblers

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Keywords

Social isolation • Well-being • Social media • Gambling

Summary

Introduction. *Gambling, especially when problematic, has been observed to have a significant impact on mental health, social relationships, and well-being in general. Social isolation and problematic social media use (PSMU) have also been identified as risk factors affecting psychological well-being, with a potential link to gambling that may intensify the impact on well-being, especially among adolescents. However, the interaction between these factors remains poorly explored, especially in younger populations. This study aims to investigate the effects of social isolation and problematic social media use on psychological well-being in a sample of adolescents, focusing on how these factors interact and influence well-being according to different engagement in gambling.*
Methods. *We analyzed data from the 2021/2022 Italian Health Behaviour in School-aged Children study in Tuscany Region. A cross-sectional study was conducted on 1,265 Tuscan adolescents aged 15-17 years, divided into three groups according to gambling behavior: non-gamblers, occasional gamblers and problem gamblers. Participants completed self-report questionnaires to assess well-being, social isolation, and PSMU. Data were analyzed using clustering methods, descriptive statistics, and path analysis to explore the relationships among these variables.*
Results. *The study identified three distinct groups of gamblers: non-gamblers (74.3%), casual gamblers (10.0%) and problem gamblers (15,7%). Contrary to expectations, problem gamblers reported the highest well-being scores, suggesting potential compensatory mechanisms or subjective perceptions masking underlying vulnerabilities. Social isolation had a negative impact on well-being in all groups, with the strongest effects observed in casual gamers. Problematic social media use did not show significant differences between groups, but was associated with lower well-being in all groups. An unexpected positive interaction between social isolation and PSMU was found in problem gamblers, indicating a unique reinforcing relationship in this group.*
Discussion. *The results highlight the complex interaction between gambling behavior, social isolation, and problematic social media use in influencing adolescents' well-being. While social isolation consistently reduced well-being, problematic gamblers showed higher well-being scores, potentially due to developmental factors or maladaptive coping mechanisms.*
Conclusion. *The study emphasizes the need for further research to better understand these relationships, particularly in the context of online gambling and social media use, to provide targeted interventions for at-risk adolescents.*

Introduction

The relationship between gambling behavior and well-being

Gambling, in its various forms, has significant and multifaceted effects on well-being, influencing mental health, social relationships, and overall life satisfaction. Studies have shown that individuals with pathological gambling tendencies tend to experience poorer overall well-being compared to those with more moderate or recreational gambling habits [1]. Research highlights that as the severity of problem sports betting increases, so too do mental health symptoms across multiple domains [2]. This may be due to the negative consequences associated with problem gambling, such as financial difficulties, relationship strain, and mental health issues [3]. Conversely, those who engage in gambling at a lower intensity may not experience the same degree of well-being impairment.

Beyond mental health, the negative effects extend to life satisfaction and connectedness, with social functioning showing lower levels as gravity of problematic gambling increases. These findings underscore the pervasive impact of problem gambling on both individual mental health and broader social integration [2].

Among adolescents, problem gambling and gaming share common risk factors, such as low parental monitoring, distrust in societal norms, and male gender. However, distinct pathways to these behaviors also emerge. For gambling, higher approval from peers and family, coupled with lower social support, predicts increased severity, whereas poor family functioning and younger age are more indicative of gaming problems.

Both behaviors correlate with diminished well-being, but problem gaming appears uniquely linked to direct declines in life satisfaction, potentially reflecting its role as a maladaptive coping mechanism [4].

On the contrary, some studies examining broader populations confirm that gambling's effects on well-being are cumulative. Recreational gamblers maintain happiness levels comparable to non-gamblers, suggesting that gambling as a leisure activity does not inherently harm well-being. However, as gambling behavior escalates to "at-risk" or pathological levels, marked reductions in happiness become evident. The transition from social to at-risk gambling corresponds to a sharp 22% drop in well-being, with pathological gamblers exhibiting the lowest life satisfaction. The damage extends beyond financial or legal consequences, encompassing emotional distress, family strain, and social isolation [5].

Taken together, these findings illustrate how gambling behaviors, particularly as they progress into problematic or pathological domains, profoundly disrupt mental health and social well-being. The effects are not limited to immediate psychological distress but also manifest in reduced life satisfaction, diminished connectedness, and impaired social functioning. The most severe consequences, such as heightened anxiety, depression, and loneliness, align with a consistent decline in subjective well-being, as measured by happiness, life satisfaction, and social integration [2, 4, 5].

Gambling behavior and social isolation

Social isolation, defined as the lack of meaningful social interactions or connections, has profound effects on psychological and physical well-being. One of the leading theories is Vaux's (1988) Social Support Theory, which emphasizes that social support -- understood as material, psychological and emotional resources available through interactions with other people -- is essential for coping with stressful events. According to this theory, social isolation is considered a risk factor for psychological well-being because it deprives individuals of resources that are essential for coping with stressful situations or for maintaining emotional and psychological balance [6].

The "Tend and Befriend" theory by Taylor et al. [7] highlights the importance of social connections as a natural stress response. When feeling isolated or threatened, the body triggers mechanisms to seek closeness and protection, helping restore emotional balance. Social isolation negatively impacts mental and physical health, increasing anxiety, depression, stress, and reducing life satisfaction [8].

Literature shows how it is associated with increased risks of mental health disorders such as anxiety, depression, and stress, as well as cognitive decline and reduced life expectancy. The absence of social support can exacerbate feelings of loneliness and hopelessness, leading to maladaptive coping mechanisms, such as substance use or addictive behaviors, as individuals attempt to mitigate their emotional distress. Research has consistently shown that social isolation disrupts emotional regulation and fosters vulnerabilities to compulsive behaviors by weakening the protective effects of interpersonal relationships. These effects are pervasive across different cultural, social, and economic backgrounds, emphasizing the universal importance of social connectedness for overall health and stability [9, 10].

Some studies conducted during the pandemic of COVID-19 show the effects of social isolation on gambling behavior. Social isolation heightened psychological vulnerabilities, such as anxiety, stress, and loneliness, which, in turn, impacted gambling behaviors, particularly among individuals already predisposed to gambling issues. For instance, one study found that men and individuals with prior gambling experiences reported higher gambling scores during the pandemic, with no significant correlation between psychological stress and gambling behaviors, suggesting that pre-existing gambling tendencies played a more critical role than the direct effects of isolation [11]. A longitudinal study in Sweden similarly showed that worries about mental health during the pandemic significantly increased gambling frequency and gambling problems, particularly in high-risk games like online casinos, indicating that psychological distress amplified problematic gambling among vulnerable populations [12]. Cultural differences were also observed, as loneliness in Finland strongly correlated with excessive gambling and participation in online gambling communities, whereas in the U.S., gambling behaviors were less influenced by isolation and more by individual gambling tendencies [11, 12].

Gambling can impact social connections, with problematic gamblers often feeling more isolated and perceiving less support from family and friends due to preoccupation with gambling, social withdrawal, and relationship issues. Conversely, those with controlled gambling tend to maintain stronger social ties, reducing negative social effects [3].

These findings collectively demonstrate that social isolation exacerbates gambling behaviors indirectly by intensifying psychological vulnerabilities and emotional distress, rather than acting as a direct trigger, particularly in high-risk populations and cultural contexts [11, 12].

Gambling behavior and pathological social media use

The rise of digital technologies, including social media, has also been linked to the development of problematic gambling behaviors, particularly among younger populations [13]. Modern digital environments foster addictive tendencies by offering constant engagement, reinforcing impulsive behavior, and exposing users to emotionally charged content. These dynamics have significant psychological effects, including increased emotional distress, impulsivity, and vulnerability to compulsive behaviors such as gambling. This interplay is further intensified by overlapping risk factors that exacerbate these issues and create a self-reinforcing cycle of maladaptive behavior. Individuals with pathological gambling tendencies may exhibit increased engagement

in social media platforms, potentially using these digital spaces as a means of coping with or escaping from the negative consequences of their gambling activities [14].
One study by Akbari et al., using latent profile analysis, identified distinct clusters of problematic social media users and demonstrated their links to gambling and well-being. High-risk individuals for PSMU were found to be more likely to engage in problematic gambling behaviors, with these behaviors linked to low levels of emotional well-being and increased social isolation. Social media often serves as a medium through which gambling behaviors are intensified, either by fostering easy access to betting opportunities or by promoting gambling advertisements, which capitalize on the same emotional vulnerabilities fueling excessive social media use. Individuals engaging heavily in both PSMU and gambling often exhibited elevated symptoms of anxiety, depression, and diminished self-esteem. These psychological impacts are not isolated but interrelated; problematic social media use creates emotional distress that can drive individuals toward gambling for short-term relief, while gambling, in turn, leads to further stress and emotional dysregulation. The cyclical and reciprocal nature of these behaviors underscores their deeply rooted connections within the broader spectrum of compulsive and addictive tendencies [15, 16].
Similarly, Tullett-Prado et al. [17] delved into the psychological mechanisms behind PSMU and its ties to gambling and found a cyclical relationship wherein excessive social media use escalates impulsivity, social disconnection, and emotional distress, driving individuals toward gambling as a form of escapism or emotional regulation. In turn, gambling behaviors exacerbated these emotional challenges, creating a self-reinforcing feedback loop. The findings underline that these intertwined behaviors lead to a host of negative outcomes, including diminished self-regulation and compounding emotional stress.
Moreover, research shows that emotions such as guilt, shame, and impulsive reactions frequently found in posts were strong predictors of gambling problems. The researchers leveraged machine learning models like EmoBERTa to detect these emotional indicators, finding that the evolution of emotional states over time provided critical insights into gambling behaviors. Furthermore, social media itself can act as a catalyst for these emotions, intensifying negative feelings through exposure to curated and emotionally charged content, which may escalate gambling behaviors as a form of escapism or coping mechanism [16].
In summary, problematic social media use and gambling behaviors are intricately linked, both influencing and amplifying one another. Their interplay is characterized by shared psychological vulnerabilities, reinforced through digital environments that exploit emotional triggers and impulsivity.
Also, social isolation and problematic social media use emerge as interconnected factors that may significantly influence susceptibility to problem gambling. Social isolation, described as the reduction or absence of meaningful relationships, deprives individuals of the social support needed to cope with stressful events and reduces psychological resilience [6]. This lack of connection can lead to a search for compensatory alternatives, such as gambling, which offers a sense of stimulation, belonging, and immediate reward. However, gambling, often accessed through online platforms, can exacerbate isolation and reinforce a vicious cycle of social alienation and behavioral addiction [18].
Similarly, problematic social media use, characterized by compulsivity and loss of control, shares many similarities with problem gambling in terms of underlying mechanisms. Both behaviors are driven by dopaminergic reward mechanisms that incentivize repetitive use despite negative consequences [19]. The pervasive and highly addictive nature of social platforms and gambling apps makes individuals already predisposed to isolation or addiction particularly vulnerable. Problematic use of social media can act as a gateway to online gambling, particularly through social games with microtransaction or virtual betting components that often mask traditional gambling mechanisms [20].
In addition, negative emotions such as anxiety and depression, compounded by social isolation or problematic social use, have been shown to contribute to pathological gambling as an escapism or emotional regulation strategy [21]. People who are isolated or dissatisfied with real social relationships may be driven toward gambling activities to feel temporarily more connected, gaining positive reinforcement in the short term but at the cost of worsening mental and financial health in the long term.
Despite what emerges from the literature, it is observed that there are currently no studies defining the relationship between well-being, social isolation, pathological use of social media and gambling.
This cross-sectional study focuses on the impact of digital and relational dynamics on individual well-being. The research stems from the observation that social isolation and social media use can significantly influence our psychological state, with consequences varying depending on personal contexts. The primary objective is to understand how social isolation and problematic social media use interact and influence psychological well-being. Researchers aim to explore the complex relationships between these factors, going beyond simple direct effect measurements to investigate more subtle and hidden interactions.

Methods

Participants

A total of 1,265 Tuscany students aged between 15 and 17 years took part in the study. Data were collected during 2022, within the Health Behaviour in School-aged Children (HBSC) survey, a WHO collaborative cross-national study of adolescent health and well-being. Data collection involved the recruitment of a two-stage stratified sample of classes and grade levels that

represent the regional, economic, and public-private distribution of schools in Italy [22, 23]. Before data collection, students' parents received an information note describing the survey's purpose. Families could deny participation by filling in and returning the note to the teachers in each class involved. The study was conducted according to the guidelines of the Declaration of Helsinki. In 2022, the Italian HBSC study protocol and questionnaire were formally approved by the Ethics Committee of the Italian National Institute of Health (Ref. PROT-PRE876/17, 20 November 2017). According to the WHO classification, the majority of the population (82.9%) fell into the normal weight category, while a smaller percentage was classified as overweight (12.1%) or obese (2.8%), together accounting for about 15% of the population. Lastly a very few individuals were underweight, comprising just 2.1%.

Procedures and materials

Participants were asked to fill out a self-report questionnaire aimed at assessing a wide range of topics related to health behaviors in young people. This study considered only a small part of the information collected with HBSC: in particular, data about well-being, level of social isolation, presence of problematic social media use, and finally, gambling. Few demographic information were also considered: age, gender, and Body Mass Index (BMI).

To explore the presence or absence of gambling behavior in the past year and lifetime, 2 items on a 7-point Likert scale were used, where scores were as follows 1 = never; 2 = 1-2 times; 3 = 3-5 times; 4 = 6-9 times; 5 = 10-19 times; 6 = 20-39 times; 7 = 40 times and more.

Additionally, two dichotomous questions from the Lie/Bet questionnaire (Johnson et al., 1998) were used to analyze gambling behavior: the first explained the lying behavior, and the second expressed the need to bet more.

To assess well-being, the WHO Well-being Index [24] was used, which explores positive moods, vitality, and general interests. This instrument consists of 5 items on a 6-point likert scale from 0-5 where 0 indicates "at no time" and 5 indicates "all the time".

Next, four items were introduced to assess social isolation, specifically feelings of exclusion and isolation and lack of companionship. Responses are distributed on a 5-point Likert scale where 1 indicates "never" and 5 indicates "always". The Cronbach's Alpha resulting from the analysis was 0.883.

Finally, pathological social media use was assessed using the Italian version of the Social Media Disorder scale [25]. Respondents were asked to answer Yes or No to nine items referring to addiction-like symptoms experienced in the past 12 months (*i.e.,* salience, tolerance, withdrawal, persistence, conflict, escape, deception, problems in important life domains and displacement of activities.

Analysis

First, descriptive analyses were conducted on the study sample to summarise data. Subsequently, the four questions related to gambling behavior were analysed by a clustering method (TwoStep), which provided the participant's profile according to the levels of gambling presented. A non-parametric test (Kruskal-Wallis) was used to compare the levels of well-being, social isolation and pathological social media use among the clusters. Finally, a path analysis was conducted to determine the effect of the relationships between social isolation and problematic social media use on well-being in the three population clusters resulting from the analysis above. Analyses were conducted using SPSS and Jamovi 2.6.2 software. The level of significance was set at $p<0.05$.

Results

A total of 1,265 Tuscany students aged between 15 and 17 years took part in the study. The mean age of the sample was 16 years (sd = 1). Of these, the majority were female (51.7%) and the remainder were male (48.3%). According to the WHO classification, the majority of the population (82.9%) fell into the normal weight category, while a smaller percentage was classified as overweight (12.1%) or obese (2.8%), together accounting for about 15% of the population. Lastly very few individuals were underweight, comprising just 2.1%.

Three groups of participants emerged from the analysis of gambling behavior, which differed in terms of patterns and levels of gambling behavior (Tab. I). Cluster 1, which comprises the largest group (74.3%, n = 940), is characterized by individuals who reported no gambling activity either in their lifetime or in the past 12 months. This group also does not show dysfunctional behaviors related to gambling, such as lying or the need to bet more.

Cluster 2, representing 10.0% of the sample (n = 127), includes individuals with minimal involvement in gambling, all of whom reported 1-2 gambling occasions in their lives. In the past 12 months, 46.5% of this group gambled 1-2 times, while the remaining 53.5% reported no gambling activity. Again, subjects in this group denied in all cases that they had lied about gambling or felt the need to bet more, indicating limited and potentially recreational gambling activity with no signs of problem behavior.

In contrast, Cluster 3 (15.7%, n = 198) showed more frequent and potentially problematic gambling behaviors. Lifetime gambling activity in this cluster was significantly higher, with 32.8% reporting having gambled 3-5 times, 16.2% reporting having gambled 6-9 times, and 14.6% reporting having gambled 40 times or more. Gambling behavior in the past 12 months followed a similar pattern, with 27.3% playing 1-2 times, 22.2% playing 3-5 times, and 9.1% playing 40 times or more. In addition, 12.6% of individuals in this cluster admitted to lying about their gambling behavior and 16.2% reported feeling the need to bet more, indicating psychological and behavioral patterns often associated with gambling problems. These results highlight the heterogeneity of gambling behavior in the sample, with Cluster 3 representing the highest risk group for gambling related problems.

Tab. I. Differences between the three clusters in relation to gambling behavior.

		Cluster 1 N (%)	Cluster 2 N (%)	Cluster 3 N (%)	Total N (%)
Lifetime	Never	940 (100.0)	0 (0.0)	0 (0.0)	940 (74.3)
	1-2 times	0 (0.0)	127 (100.0)	12 (6.1)	139 (11.0)
	3-5 times	0 (0.0)	0 (0.0)	65 (32.8)	65 (5.1)
	6-9 times	0 (0.0)	0 (0.0)	32 (16.2)	32 (2.5)
	10-19 times	0 (0.0)	0 (0.0)	35 (17.7)	35 (2.8)
	20-39 times	0 (0.0)	0 (0.0)	25 (12.6)	25 (2.0)
	40 times or more	0 (0.0)	0 (0.0)	29 (14.6)	29 (2.3)
Total		940 (100.0)	127 (100.0)	198 (100.0)	1265 (100.0)
Last 12 months	Never	940 (100.0)	68 (53.5)	16 (8.1)	1024 (81)
	1-2 times	0 (0.0)	59 (46.5)	54 (27.3)	113 (9)
	3-5 times	0 (0.0)	0 (0.0)	44 (22.2)	44 (3.5)
	6-9 times	0 (0.0)	0 (0.0)	23 (11.6)	23 (1.8)
	10-19 times	0 (0.0)	0 (0.0)	23 (11.6)	23 (1.8)
	20-39 times	0 (0.0)	0 (0.0)	20 (10.1)	20 (1.6)
	40 times or more	0 (0.0)	0 (0.0)	18 (9.1)	18 (1.4)
Total		940 (100.0)	127 (100.0)	198 (100.0)	1265 (100.0)
Lying behaviour	No	940 (100.0)	127 (100.0)	173 (87.4)	1240 (98.0)
	Yes	0 (0.0)	0 (0.0)	25 (12.6)	25 (2.0)
Total		940 (100.0)	127 (100.0)	198 (100.0)	1265 (100.0)
Need to bet more	No	940 (100.0)	127 (100.0)	166 (83.8)	1233 (97.5)
	Yes	0 (0.0)	0 (0.0)	32 (16.2)	32 (2.5)
Total		940 (100.0)	127 (100.0)	198 (100.0)	1265 (100.0)

Tab. II. Comparison of the three clusters among the measurement scales.

	Cluster 1		Cluster 2		Cluster 3			
	Mdn (IQR)	M (sd)	Mdn (IQR)	M (sd)	Mdn (IQR)	M (sd)	Test statistic*	p
Well-being	48 (32)	48.36 (20.48)	52 (28)	51.50 (19.53)	54 (20)	54.93 (16.22)	18.806	0.000
Social isolation	8 (6)	8.87 (3.88)	8 (6)	8.51 (3.48)	7 (6)	7.62 (3.49)	18.582	0.000
Pathological social media use	2 (4)	2.47 (2.44)	2 (3)	2.35 (2.04)	2 (4)	2.22 (2.16)	1.934	0.380

* Two-tails Kruskal-Wallis test

In conclusion, we can state that the data reveal that cluster 1 represents individuals who abstain from gambling or engage in it to a minimal extent, without showing signs of problem behavior. Cluster 2 shows limited gambling activity in which the first signs of risk may emerge. Finally, Cluster 3 emerges as the most at-risk group, with a considerable proportion of problem gambling-associated behavior, such as dishonesty and the urge to gamble more.

Table II compares the scores of the three scales (well-being, social isolation, and problematic social media use) among the three student groups.

The data indicate a gradual improvement in well-being between clusters, with statistically significant differences between them ($p = 0.000$). Subjects in Cluster 1 show lower wellbeing scores (Mdn = 48; M = 48.36; sd = 20.48), suggesting that this group may have issues that affect general wellbeing.

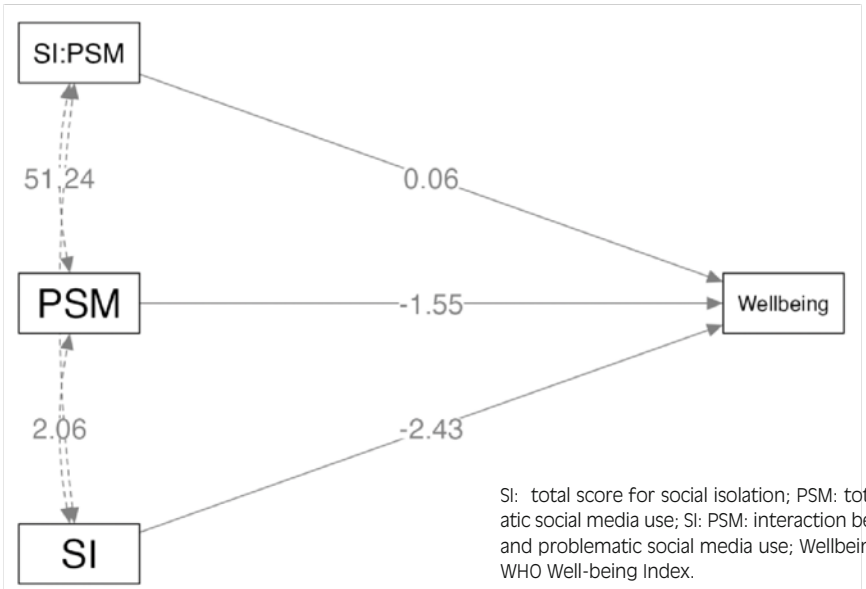
Looking at Cluster 2 we note a slight improvement (Mdn = 52; M = 51.50; sd = 19.53), indicating moderate levels of well-being. Finally, subjects in Cluster 3, the most at-risk group, report the highest well-being scores (Mdn = 54; M = 54.93; sd = 16.22), which could suggest the presence of compensatory mechanisms or a subjective perception of well-being disguising underlying vulnerabilities.

With regard to social isolation, the scores also differ significantly between the clusters ($p = 0.000$), with Cluster 3 reporting the lowest levels of social isolation, (Mdn = 7; M = 7.62; sd = 3.49) despite being at high risk for gambling. Contrary to what is reported in the literature, the data show that Cluster 1, *i.e.,* those at lower risk or with no gambling, show higher scores on the social isolation rating scale (Mdn = 8; M = 8.87; sd = 3.88). This paradox might reflect stronger social ties or specific gambling-related social dynamics that are established when the person engages in gambling, whether in presence or online.

Lastly, the data on pathological use of social media show that there are no statistically significant differences between the groups ($p = 0.380$), suggesting similar levels of use in all three clusters.

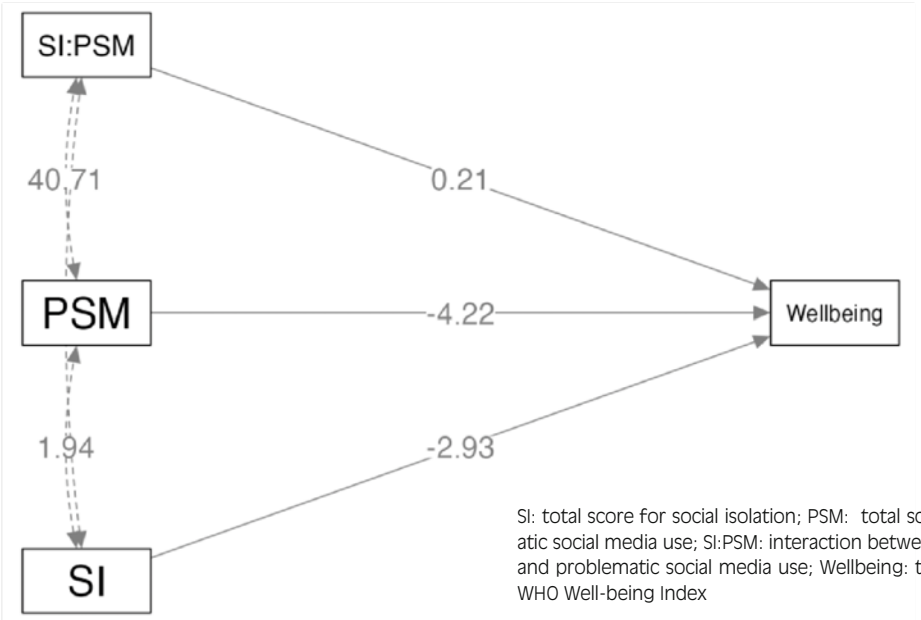
Interesting results can be observed from the path analysis, which show some differences with the data

Fig. 1. Effect of social isolation and problematic social media use on wellbeing for Cluster 1.



SI: total score for social isolation; PSM: total score for problematic social media use; SI: PSM: interaction between social isolation and problematic social media use; Wellbeing: total score on the WHO Well-being Index.

Fig. 2. Effect of social isolation and problematic social media use on wellbeing for Cluster 2.

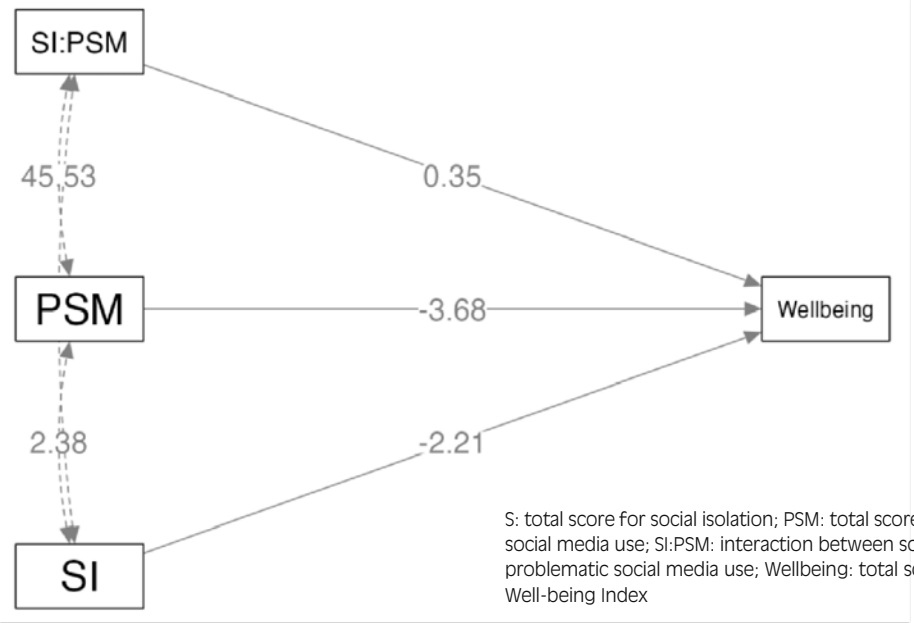


SI: total score for social isolation; PSM: total score for problematic social media use; SI:PSM: interaction between social isolation and problematic social media use; Wellbeing: total score on the WHO Well-being Index

in the literature. With regard to cluster 1 (Fig. 1), the results indicate a significant relationship between social isolation and well-being, where increasing levels of social isolation are associated with decreasing well-being scores (estimate = -2.4311, $p < 0.001$). Similarly, a significant negative relationship is observed between problematic social media use and well-being, where higher levels of problematic social media use correspond to lower well-being scores (estimate = -1.5532, $p = 0.016$). However, the interaction between social isolation and problematic social media use (SI_total_score: PSM_total_score) does not demonstrate a statistically significant effect, suggesting that the combined influence of these two factors does not significantly impact well-being scores (estimate = 0.0630, $p = 0.328$).

In cluster 2 (Fig. 2), greater effects of social isolation on well-being are observed, in fact higher levels of social isolation are associated with lower well-being scores (estimate = -2.9343, $p < 0.001$). The same applies to problematic social media use, which shows a significant negative relationship with well-being, therefore higher levels of problematic use are associated with lower well-being scores (estimate = -4.2239, $p = 0.024$). Again, the interaction term between social isolation and problematic use of social media (SI_total_score:PSM_total_score) has a positive effect on well-being, but does not reach

Fig. 3. Effect of social isolation and problematic social media use on wellbeing for Cluster 3.



S: total score for social isolation; PSM: total score for problematic social media use; SI:PSM: interaction between social isolation and problematic social media use; Wellbeing: total score on the WHO Well-being Index

statistical significance (estimate = 0.2069, p = 0.302), suggesting that there is no notable combined influence of these two factors on well-being.

Finally, in cluster 3 (Fig. 3), a significant negative effect of both social isolation (β = -2.2074, p < 0.001) and problematic social media use (β = -3.6772, p = 0.002) on well-being was observed, indicating that each factor, independently, was associated with decreased levels of well-being. However, the interaction analysis produced an unexpected positive relationship between these variables (β = 0.3535, p = 0.006). This interaction effect suggests that when social isolation and problematic social media use were present simultaneously, their combined impact on well-being was less detrimental than would be predicted by their individual negative effects. In particular, participants who reported high levels of social isolation and problematic social media use had relatively higher well-being scores than would be expected given the negative main effects of these factors taken individually.

Discussion

The results of this study provide interesting information on the complex interplay between gambling behaviour, social isolation, problematic social media use and psychological well-being.

One of the main similarities between our results and those in the literature is the negative impact of social isolation on well-being. Consistent with Vaux's [18] social support theory and the findings of Holt-Lunstad et al. [9], our study found that social isolation significantly reduces well-being across all clusters. This is in line with the wider literature, which consistently highlights the negative effects of social isolation on mental health, including increased anxiety, depression and reduced life satisfaction [6, 8].

However, our results also present some notable differences from literature. Contrary to expectations, the highest-risk group of gamblers (Cluster 3) reported the highest levels of well-being, despite exhibiting problem gambling-related behaviours, such as dishonesty and increased need to gamble. This result contradicts studies linking pathological gambling to lower well-being, increased anxiety and depression [2,5]. This can be read in light of the fact that while previous research has focused primarily on adult populations, our study specifically examined adolescents between the ages of 15 and 17. This age difference is crucial, as adolescents may experience and process gambling behaviors differently from adults due to different developmental factors. During adolescence, risk behaviors, including gambling, often occur within social contexts and can be perceived as normative experiences that contribute to identity formation and peer acceptance [25]. Research has shown that adolescents are more likely than adults to engage in gambling activities for social reasons and to perceive them as a form of entertainment rather than problem behavior [26]. Unlike adults, who may gamble in isolation or suffer significant consequences in their daily lives as a result of gambling, adolescents may integrate gambling into their social activities, seeing it as a means to build peer bonds and improve their social status [27]. In addition, neuroscientific research has shown that adolescents exhibit greater sensitivity to reward and a reduced ability to assess long-term consequences than adults [28]. This developmental trait may lead adolescents to focus more on the immediate positive aspects of gambling, such as excitement, social

interaction, and winnings, rather than the potential negative consequences [29]. The combination of greater sensitivity to reward and less financial responsibility than adults may explain why in our sample of adolescents problem gambling does not show the same negative association with well-being observed in adult populations [30]. Finally, another possible explanation involves compensatory mechanisms or a subjective perception of well-being that masks underlying vulnerabilities. Studies have shown that adolescents with problem gambling behaviors often use gambling as a maladaptive coping mechanism to regulate negative emotions and stress [21]. This coping strategy may be particularly relevant during adolescence, when emotional regulation skills are still developing and alternative coping mechanisms may be limited [31]. The temporary relief provided by play activities could help increase perceptions of well-being, even in the presence of problem behaviors. This is in line with Blaszczynski and Nower's [21] pathways model, which suggests that gambling may serve as an emotional regulation strategy for individuals experiencing psychological distress. Factors that may influence gambling behavior include parenting style. An authoritative and forgiving parenting style, characterized by warmth, acceptance and involvement, may be a protective factor, reducing the likelihood of gambling [32, 33]. In contrast, authoritarian parenting, characterized by severity and punitive practices, and neglectful parenting, defined by low involvement and emotional support, are associated with a higher risk of gambling [34]. Adolescents from authoritarian families are more likely to exhibit gambling-related problems, such as craving and loss of control, while those with neglectful parents may develop gambling behaviors to compensate for unmet emotional needs.

Another unexpected outcome was the higher level of social isolation reported by Cluster 1, the group with minimal or no involvement in gambling. This contradicts the literature, which usually associates lower involvement in gambling with stronger social ties and support systems [3]. Several developmental factors may explain this unexpected relationship, *e.g.,* adolescents who do not gamble, by not participating in socialization opportunities where gambling is a bonding mechanism, may find themselves isolated from the peer group, especially at a developmental stage when peer acceptance is critical for identity formation [31, 35]. In addition, their slightly elevated problematic use of social media suggests that these individuals may prefer interaction that occurs purely online, rather than interaction that occurs in person, this according to research, may intensify rather than alleviate feelings of isolation during adolescence [36, 37]. Finally, it is important to consider personality characteristics or pre-existing conditions such as introversion or social anxiety that may simultaneously promote abstention from gambling and broader social withdrawal [38].

The lack of significant differences in problematic social media use between the three groups also differs from data found in the literature, in fact, excessive social media use is often correlated with increased gambling behavior and emotional distress [14, 15]. This could be attributed to the pervasive nature of social media use across all groups, regardless of gambling behaviour, suggesting that social media use could be a universal factor influencing well-being rather than a factor solely related to gambling. Finally, no significant interaction effect was observed between social isolation and problematic social media use in non-gamblers and occasional gamblers. The interaction effect observed exclusively in problem gamblers suggests that they may experience a unique synergistic relationship between social isolation and problematic social media use, consistent with Griffiths' [39] concept of "synergy of behavioral addiction," in which multiple maladaptive behaviors mutually reinforce each other during a developmental period characterized by increased reward sensitivity and emotional reactivity [40]. Unlike their peers, problem gamblers likely employ both gambling and excessive social media use as interconnected maladaptive coping strategies, creating a combined negative effect on well-being. In contrast, non-gamblers and casual gamblers appear to have developed more effective self-regulatory mechanisms that keep these risk factors functionally separate [41], aligning with Jessor's [42] theory of problem behavior, which views casual gambling as a potentially normative adolescent experimentation rather than a psychopathology. This developmental interpretation finds further support in neurobiological research indicating that adolescents with problem gambling show distinct neural responses to social exclusion [43] and in studies of peer relationships showing that problem gamblers often attend social environments in which multiple risk behaviors are normalized and reinforced together [44]. Furthermore, according to theories of personal predispositions, problem gamblers may possess temperamental characteristics that make them particularly responsive to social isolation and problematic social media use during this critical window of neurodevelopment, when prefrontal regulatory systems are still maturing unevenly across individuals [30, 45, 46].

In conclusion, while our findings align with the literature by highlighting the negative impact of social isolation on well-being, they also reveal unexpected patterns, particularly in the relationship between gambling behavior and well-being. These discrepancies suggest that the psychological mechanisms underlying gambling behavior and its impact on well-being may be more complex than previously understood, involving compensatory mechanisms, subjective perceptions of well-being, and social dynamics of gambling environments. Further research is needed to explore these relationships in more depth, particularly in the context of online gambling and social media use, to better understand how these factors interact with each other in influencing psychological well-being.

Limitations

Of course, our study is not without its limitations. Primary among these is the cross-sectional design, which contributes to limiting the ability to establish causal relationships between the variables. Although the results suggest the existence of associations between the variables being studied, it is not possible to determine whether social isolation or problematic social media use directly lead to changes in well-being or gaming behavior, or vice versa. Longitudinal studies would be needed to explore these causal pathways over time.

Secondly, relying on self-report questionnaires introduces the potential for response bias. Participants might underestimate or overestimate their gambling behavior, social isolation or problematic social media use due to social desirability or recall bias. This is particularly relevant given the sensitive nature of gambling and the potential stigma associated with problematic behavior.

Another limitation is the homogeneity of the sample, composed mainly of adolescents between the ages of 15 and 17. Although this age group is particularly relevant for studying the early development of gambling and social media-related behavior, the results may not be generalisable to older populations. For example, the relationship between social isolation and gambling behavior might be different in adults who have more established social networks or financial responsibilities. Expanding the sample to include a wider age range and different demographic groups would improve the generalisability of the results.

The clustering method used to classify participants according to gambling behavior, while useful for identifying distinct patterns, may also oversimplify the complexity of gambling behaviors. The three clusters (non-gamblers, low-risk gamblers and high-risk gamblers) do not capture the full spectrum of gambling severity or the nuances of individual differences within each group. For example, the high-risk group (Cluster 3) included individuals with varying degrees of problem behavior, from those who gambled occasionally to those who exhibited more severe symptoms of pathological gambling. A more specific approach, such as using continuous measures of gambling severity, could provide a more detailed understanding of the relationships between gambling behavior and well-being. Finally, the study did not take into account potential confounding variables that could influence the observed relationships, such as personality traits, mental health history, or family dynamics. For example, individuals with preexisting mental health conditions, such as anxiety or depression, might be more susceptible to both social isolation and problem gambling, which could confound the results. Future research should consider incorporating these variables into the analysis to better isolate the effects of social isolation and problematic social media use on well-being.

In conclusion, although this study contributes to the growing literature on gambling behavior and its impact on well-being, we still know little about the interaction effects of social isolation and problematic social media use on these phenomena. The limitations of our study highlight the need for further investigation with respect to these variables and others that may influence the effect gambling has on well-being.

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Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethical Board of the National Institute of Health (General protocol: PRE-876/17) on 10 November 2017.

Consent to participate

Informed consent was obtained from all subjects involved in this study.

Conflicts of interest statement

The authors have explicitly stated that thet have no known financial interests or personal affiliations with third parties that could potentially impact the outcome of this study.

Availability of data and material

Data presented in this study are available in accordance with the 2022 Italian HBSC data access policy. Requests should be directed to the Italy Principal Investigator, Prof. Giacomo Lazzeri: giacomo.lazzeri@unisi.it.

Authors' contributions

FM, FF: Conceptualization; Formal analysis; Writing-original draft; and Writing-editing. NC, MC: Writing-review & editing. UA: Data Curation. GL: Conceptualization; Data curation and Writing-review & editing.

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HEALTH PROMOTION

Assessment of Knowledge and Practices Related to Children's Physical Fitness and Health Among French PE Teachers

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Keywords

Physical fitness • School • Physical education • Teachers • Health

Summary

Objectives. *To assess PE teachers' knowledge of physical fitness and its link to children's health and identify barriers and facilitators for its management in schools.*
Methods. *A total of 2,378 PE teachers (56% men) completed an online questionnaire on their knowledge, perceived barriers, and facilitators regarding physical fitness.*
Results. *Most of teachers reported being aware of the associations between cardiorespiratory fitness (CRF) (96%) and muscular strength (MS) (88%) with current health in youth. A smaller proportion of teachers acknowledged knowing the potential associations of these fitness components with future health in adulthood, specifically 40% for CRF and 22% for MS. The majority of teachers (80%) reported being sufficiently trained during their training courses to assess and develop the CRF. Only 50% of teachers reported feeling sufficiently trained to assess MS, while 58% reported being adequately trained to develop this component. Among the teachers, 82% reported that insufficient practice time, large class sizes, and high heterogeneity are key obstacles. Less than 50% identified other prioritized objectives as barriers, while 30% reported a lack of material resources as a significant limitation. Then, 84% of teachers reported being interested in participating in continued professional development focused on the promotion of physical fitness in youth through PE.*
Conclusions. *Barriers such as limited training, structural constraints, and low awareness of MS recommendations hinder effective fitness management. Addressing these through improved curricula, teacher training, and resources is crucial to enhancing youth fitness and health in France.*

Introduction

For many years, robust and consistent evidence has highlighted the importance of physical fitness in youth as a key determinant of both current and future health [1]. Physical fitness encompasses several components, including cardiorespiratory fitness, musculoskeletal fitness (muscular strength, power, endurance, and flexibility), motor fitness (agility, speed of movement, balance and coordination), and body composition. Among these components, cardiorespiratory fitness and muscular strength have been widely studied and have shown the strongest and most consistent associations with health in children and adolescents [1].

Cardiorespiratory fitness (CRF) has been found to be strongly and consistently associated with significant health outcomes, including reduced adiposity, lower risk of obesity, cardiovascular risk factors, and cancer, as well as improved mental health during childhood and adolescence [1]. The benefits of high physical fitness during this period extend into adulthood. A systematic review and meta-analysis demonstrated that a higher levels of CRF are associated with a reduced risk of developing obesity and cardiometabolic disease later in life [2]. Moreover, a large Swedish prospective study revealed that low CRF in late adolescence is associated with an increased risk of chronic cardiovascular disease-related disability and predicts severe, irreversible health conditions adulthood, as reflected by higher rates of disability pensions [3, 4]. Muscular strength has also been consistently and strongly linked to important health outcomes during childhood and adolescence, and is similarly associated with health status in adulthood [1, 5-7]. Several large cohort studies have demonstrated that lower muscular strength in youth is associated with a higher risk of physical disability and increased all-cause and cause-specific (cardiovascular and cancer) mortality in later life [8, 9]. A recent study further explored the combined impact of these two components of physical fitness [7]. The authors found that adolescents with both high CRF and high muscular strength had a significantly lower risk of coronary atherosclerosis, particularly severe coronary stenosis, nearly 40 years later [7].

This evidence highlighting physical fitness as a powerful marker of health in youth emphasizes the need to improve

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or maintain high physical fitness levels in children and adolescents. However, temporal trends in physical fitness among French youth are concerning. Recently, Vanhelst et al. (2024) reported a significant decline in CRF levels, as assessed by the 20-m shuttle run test, in 15,420 French children and adolescents between 1999 and 2022 [10]. Another study examining trends in muscular strength showed a negligible decline in mean lower limb strength (assessed using the standing broad jump) and a slight improvement in mean upper limb strength (assessed using handgrip strength) among French youth from 1999 to 2023 [11]. Furthermore, both studies indicated that these trends were not consistent across the population, with data suggesting an increasing gap between low and high performers over time [11]. To address these findings, national public health initiatives are urgently needed to monitor physical fitness levels and implement programs aimed at improving physical fitness in French youth.

Children and adolescents spend a significant amount of time at school, making it an ideal environment to provide opportunities for all students, regardless of socioeconomic background, to enhance their physical fitness. Two systematic reviews and meta-analyses have shown that school-based interventions can effectively improve CRF and muscular fitness in children and adolescents [12, 13]. Within the school setting, physical education (PE) curricula appear to be the most effective avenue for assessing and promoting physical fitness. Despite this context, there is a lack of research into the knowledge levels of PE teachers and their subsequent suitability to teach health-related PE [14]. However, PE teachers in North America and Australia have reported barriers to implementing fitness assessments and interventions in their lessons, including insufficient facilities, limited confidence, and time constraints [15]. In Europe, Cox et al. highlighted a poor understanding of muscular fitness activities among UK PE teachers [16]. Currently, there is no data available on the knowledge or capacity of French PE teachers to assess and develop physical fitness in children and adolescents, and these aspects are not prioritized in French school policies.

Therefore, the primary aim of this study was to assess the physical education teachers' knowledge of physical fitness and its association with health in children. The secondary objective was to identify barriers and facilitators to improving the management of physical fitness in the school setting. We also aimed to determine whether duration of teaching experience and sex might influence knowledge of physical fitness and the perceived barriers to implementing effective strategies for promoting physical fitness in schools.

Methods

Study design and participants

This study employed a cross-sectional design targeting a sample of French PE teachers. Data were collected through an online survey conducted between October 2023 and June 2024. To reach potential participants, all regional academic institutions (n = 30) across France were contacted. These institutions then reached out to middle and high school principals and headteachers. The institutions were informed about the objectives of the study and asked to share the survey link with their PE teachers. From a total of 29,725 PE teachers in France, 2,378 participated in the present study.

This study did not involve any intervention, and was conducted on a volunteer basis. In this context, written informed consent was not required according to French human research regulations. The answers provided by PE teachers were anonymous and confidential. The data collection process was approved by the French National Commission of the Informatics Personal Data (CNIL).

Questionnaire

The questionnaire was developed by a group of experienced professionals in the fields of sport science, physical education, and educational research. The team included PE teachers, researchers specializing in physical fitness, and experts in questionnaire design. Before data collection, a preliminary version of the questionnaire was tested with a small sample of 10 secondary school PE teachers to evaluate the clarity, relevance, and length of the questions. This pretest allowed the identification of any ambiguities and helped ensure the comprehensibility and acceptability of the instrument. Following this, a pilot study was conducted with 15 additional PE teachers to assess the response quality and completion rates for each question. Items with a completion rate below 80% were reviewed and either revised or removed as necessary. After each stage, adjustments were made to improve the instrument, resulting in the final version of the questionnaire.

The final questionnaire consisted of 28 questions divided into four parts: (*i*) Teacher profile: information regarding the participant's teaching background, experience, and current teaching context (*e.g.,* type of school, years of teaching experience); (*ii*) Cardiorespiratory fitness: questions focused on teachers' perspectives and practices regarding the assessment and development of cardiorespiratory fitness in children and adolescents; (*iii*) Muscular strength: questions focused on teachers' perspectives and practices regarding the assessment and development of muscular strength in children and adolescents; (*iv*) Global objectives: questions addressing overall teaching priorities, obstacles, and facilitators in promoting physical fitness among children and adolescents, as well as their interest in further training or additional resources.

In the section on teacher profiles, demographic and professional information was collected, such as gender, years of teaching experience, and type of school (*e.g.,* middle school or high school). The cardiorespiratory fitness and muscular strength sections investigated teachers' knowledge, confidence, and practices in assessing and developing these physical fitness components, as well as their perceptions of trends in youth fitness over the past 20 years.

Participants answered questions using Likert scales

(*e.g.,* "Strongly Disagree" to "Strongly Agree"), multiple-choice options, and binary formats (*e.g.,* "Yes/No"). Specific questions allowed for multiple responses when addressing perceived correlations (*e.g.,* between cardiorespiratory fitness or muscular strength and health outcomes) or barriers to implementing physical fitness programs.

The questionnaire was preceded by an informative letter explaining the objectives of the survey and assuring participants that all data would remain strictly anonymous/confidential.

Statistical analysis

Continuous variables are presented as means (standard deviation, SD), while categorical variables are expressed as frequencies (percentages). The normality of distributions was assessed using histograms and the Shapiro-Wilk test. The results of the questionnaires are expressed as the percentages of participating teachers who answered each item. The χ^2 test was used to compare differences between sexes and levels of experience among teachers. Data were analyzed using R statistical software (version 3.2.1). A p-value of < 0.05 was considered significant.

Results

Demographic and professional characteristics of the PE teachers are presented in Table I. Among the participants, 56% were male, with 64% teaching at the middle school level and 36% at the high school level. The mean duration of teaching experience was 19.8 ± 10.1 years.

PE teachers' knowledge regarding physical fitness and health in youth according to sex and teaching duration of experience is displayed in Table II. Most of PE teachers reported being aware of the associations between CRF (96%) and muscular strength (88%) with current health in youth. In contrast, a smaller proportion of PE teachers acknowledged knowing the potential associations of these fitness components with future health in adulthood, specifically 40% for CRF and 22% for muscular strength. The percentages were higher for knowledge of the relationships between physical fitness and mental health (Tab. II).

Significant differences were found for the sex and the teaching duration of experience (Tab. II). Men reported being more aware about the association between CRF and muscular strength with future health compared to women. The percentage of teachers with less duration of experience teaching (< 10 years) reported to be more aware about the association between physical fitness and health (current, future and mental) compared to their more duration of experienced counterparts (Tab. II).

Results from teachers' perceived training and practices for assessing and developing physical fitness in youth according to sex and teaching duration of experience are presented in Table III. Regarding CRF, the majority of PE teachers (80%) reported being sufficiently trained during their training courses to assess and develop this component. Concerning muscular strength, only 50% of PE teachers reported feeling sufficiently trained to assess it, while 58% reported being adequately trained to develop this component. About assessments, 60% of PE teachers reported performing at least one measurement of CRF a year, while only 14% reported assessing muscular strength at least once a year.

In addition, men reported to feel more sufficiently trained to assess and develop CRF and muscular strength compared to women (Tab. III). Moreover, the percentage of PE teachers who reported performing at least one assessment of muscular strength was significantly higher among those with more than a 10 years duration of experience compared to their less experienced counterparts (Tab. III).

PE Teachers' perceived barriers to improving the management of physical fitness in the school setting are presented in Table IV. Among these PE teachers, 82% reported that insufficient practice time, large class sizes, and high heterogeneity among students are key obstacles. Additionally, less than 50% identified other prioritized objectives as barriers, while 30% reported a lack of material resources as a significant limitation.

A significant difference was found based on sex, with men more frequently reporting competing priorities within the PE curriculum as a barrier compared to their women counterparts (Tab. IV). Additionally, PE teachers with less duration of experience more often reported a lack of facilities/equipment and insufficient teacher training as barriers (Tab. IV).

Regarding PE teachers' perceived facilitators to improving the management of physical fitness in the school setting, the most important were improving teaching conditions, including increasing the number

Tab. I. Characteristics of participants.

	N or mean	% of total
Sex		
Men	1 332	56
Women	1 046	44
Teaching level		
Middle school	1 522	64
High school	856	36
Geographical location		
Auvergne-Rhône-Alpes	323	13.6
Bourgogne-Franche-Comté	128	5.4
Brittany	195	8.2
Centre-Val de Loire	82	3.4
Corsica	10	0.4
Grand Est	173	7.3
Hauts-de-France	134	5.6
Ile-de-France	234	9.8
Normandy	125	5.3
Nouvelle-Aquitaine	278	11.7
Occitanie	249	10.5
Pays de la Loire	139	5.8
Provence-Alpes-Côte d'Azur	220	9.3
Overseas	88	3.7

Tab. II. PE teachers' knowledge regarding physical fitness and health in youth according to sex and duration of teaching experience (n, %).

		Sex		Teaching experience		P value*	
	Total	Men	Women	< 10 years	≥ 10 years	Sex	Experience
CRF							
Association with current health	2 307 (97)	1 280 (96)	999 (98)	463 (98)	1 823 (97)	0.07	0.198
Association with future health	962 (40)	601 (45)	345 (34)	215 (45)	763 (39)	**< 0.001**	**0.011**
Association with mental health	1 587 (66)	880 (66)	684 (67)	329 (69)	1 242 (66)	0.75	0.131
Muscular strength							
Association with current health	2 096 (88)	1 170 (88)	901 (88)	440 (93)	1 636 (86)	0.97	**< 0.001**
Association with future health	521 (22)	322 (24)	178 (17)	128 (27)	377 (20)	**< 0.001**	**< 0.001**
Association with mental health	1 115 (47)	642 (48)	456 (44)	255 (54)	848 (45)	0.07	**< 0.001**
Knowledge of WHO recommandations	272 (12)	158 (12)	112 (11)	71 (15)	199 (11)	0.49	0.007

*Chi-squared test

of PE hours per week, reducing the number of children or adolescents per class, and modifying the objectives assigned to PE lessons. Furthermore, 84% of PE teachers reported being interested in participating in continued professional development focused on the promotion of physical fitness in youth through PE. Additionally, 90% expressed a strong interest in a shared web platform that would facilitate the administration of physical fitness tests and generate personalized reports for youth.

Discussion

This study is the first large-scale survey to assess the knowledge, perceptions, and practices of French PE teachers regarding physical fitness in children and adolescents. Our main results revealed significant gaps in PE teachers' understanding of the importance of physical fitness components, particularly muscular strength, and their association with health outcomes. Moreover, while teachers recognized the importance of CRF and declared to be confident in assessing it, barriers such as limited facilities and time constraints hindered the implementation of comprehensive fitness programs. These findings are of major interest because since the 2024 Olympic Games in Paris (France), there has been increased attention on the assessment and the development of children's health-related physical fitness levels among national policymakers. Data from this study highlight the need to address the gaps and support PE teachers in promoting physical fitness. In addition to informing new school policies, easily applicable solutions should be implemented, such as integrating targeted modules on muscular strength and fitness into initial teacher education, encouraging participation in free online training (e.g., ONAPS and FitBack resources), and promoting practical workshops during continued professional development. These results could inform the development of new school policies aimed at enhancing training and resources for PE teachers to effectively promote physical fitness within the school setting.

The main finding regarding PE teachers' knowledge of physical fitness and health was that less experienced teachers were more aware of the association between muscular strength and current/future/mental health. This observation is linked to the evolution of the French training program content for PE teachers, which has been modified over the past 10 years. Recent changes have focused on health and well-being, particularly in areas such as healthy living, risk prevention related to sedentary behavior, development of psychosocial skills through physical activity including muscle development [17]. In contrast, regarding PE teachers'

Tab. III. PE Teachers' perceived training and practices for assessing and developing physical fitness in youth according to sex and teaching experience (***n,%***).

		Sex		Teaching experience		P value*	
	Total	Men	Women	< 10 years	≥ 10 years	Sex	Experience
CRF							
Sufficient training to assess	1 945 (82)	1 125 (85)	812 (80)	377 (78)	1 568 (83)	**0.005**	0.079
Sufficient training to develop	1 836 (77)	1 072 (81)	757 (74)	352 (75)	1 484 (79)	**< 0.001**	0.06
Perform at least a test assessment a year	1 426 (60)	808 (61)	613 (60)	300 (63)	1 126 (60)	0.865	0.126
Muscular strength							
Sufficient training to assess	1 141 (48)	690 (52)	451 (44)	218 (46)	926 (49)	**< 0.001**	0.200
Sufficient training to develop	1 366 (58)	833 (63)	533 (52)	265 (56)	1 104 (59)	**< 0.001**	0.311
Perform at least a test assessment a year	324 (14)	190 (14)	134 (13)	46 (10)	278 (15)	0.406	**0.005**

* Chi-squared test

Tab. IV. PE Teachers' perceived barriers to improving the management of physical fitness in the school setting (***n,%***).

		Sex		Teaching experience		P value*	
	Total	Men	Women	< 10 years	≥ 10 years	Sex	Experience
Barriers							
Insufficient practice time	1 925 (82)	1 085 (81)	840 (82)	396 (84)	1 535 (81)	0.767	0.210
Competing priorities within PE curriculum	1 100 (47)	656 (49)	444 (43)	221 (47)	881 (47)	**0.004**	0.966
Lack of facilities/equipment	716 (30)	387 (29)	329 (32)	189 (40)	530 (28)	0.112	**< 0.001**
Lack of teachers training	493 (21)	263 (19)	230 (22)	130 (27)	364 (19)	0.112	**< 0.001**
Scared of student injuries	205 (9)	121 (9)	84 (8)	44 (9)	162 (9)	0.447	0.614

* Chi-squared test

perceived training and practices to assess and develop physical fitness, the differentiating factor was not the duration of experience but the sex of the PE teachers. Men reported feeling more adequately trained to assess and develop CRF and muscular strength compared to women. This observation was already shown in the study of Cox et al. where women PE teachers were less likely to plan muscular strength [16]. This may be due to gender-based biases such as muscular strength is perceived as a more masculine activity and differing physical education learning experiences influenced by societal stereotypes, as observed in previous studies [18-22]. Less experienced PE teachers expressed a desire for more physical training facilities/equipment and additional PE teachers in settings (or decrease class sample sizes). This may be because younger, less experienced teachers would have been trained with a more modern view of training PE, have higher expectations and needs extra materials to enhance their PE programs in order to increase quality and attractiveness of PE lessons. Moreover, sports media program content exerts multiple influences on practices behaviors including the need of more and novel sport equipment to reinvent PE lessons [23]. Additionally, they are likely more motivated to perform innovative pedagogical model to offer quality lessons and, as a result, feel the need to improve teaching conditions, as previously observed by Wiyono et al. [24].

Another important finding was that the majority of PE teachers (90%) expressed a need for access to a free online platform to help the administration of physical fitness assessments and generate personalized reports for each youth evaluated. Two main actions could address this request. First, the National Observatory for Physical Activity and Sedentary Behaviors (ONAPS) has developed manuals for several physical fitness tests, including the 20m shuttle run test, handgrip strength, standing broad jump, and sit-and-reach test. These manuals provide valuable information for PE teachers, such as instructions to give to children and adolescents, required materials, methodologies suitable for the school environment, and scales for interpreting the results. These documents are available online and can be downloaded as PDFs (https://onaps.fr/boite-a-outils/evaluer/#). The second interesting tool for PE teachers is the initiative developed by the European FitBack network [25]. The FitBack project, endorsed by international fitness experts, aims to provide scientific and practitioner communities with a free online platform outlining the steps required for implementing and harmonizing physical fitness assessments and interpreting results in school settings across Europe [25]. Authors also emphasize that the FitBack platform offers guidance to prevent undesirable practices, such as grading students based on their fitness levels or encouraging fitness competitions among youth. Instead, it promotes the use of physical fitness testing as an educational tool to foster learning and understanding about fitness, its importance for health and sports, and to help children and adolescents set individual objectives for improvement [25]. The web platform is available in French version (https://www.fitbackeurope.eu/fr-fr/).

Our last finding revealed that 84% of PE teachers showed an interest in participating in continued professional development focused on promoting physical fitness in youth through PE. Similarly, the EmPOWERment survey by Cox et al. (2023) reported the same results for PE teachers in the UK regarding the delivery of muscular activity [16]. Given these results, future research is needed in France to provide continued professional development opportunities for PE teachers about the development of physical fitness in children and adolescents. These programs should focus on practical, evidence-based strategies and provide teachers with simple, accessible tools and resources that can be directly applied in schools. A group of experts will be formed soon in order to develop and offer a free online continued professional development program on this topic. A similar work was conducted in UK where authors assessed the feasibility and acceptability of an online continued professional development program to enhance PE teachers' knowledge of muscular fitness activity [26]. The authors concluded that co-producing an online CPD program can enhance knowledge and positively impact teaching practices [26].

This study has several strengths that contribute to its relevance. First, the questionnaire was rigorously developed and corrected through pretesting and a pilot study to ensure the feasibility, clarity, relevance, and comprehensibility. This systematic approach to questionnaire design strengthens the validity and reliability of the data collected. Additionally, the study provides valuable insights for policies makers into PE teachers' knowledge, practices, and perceived barriers regarding the promotion of physical fitness in schools, addressing an important gap in the literature. However, the study is not without limitations. Although the present data were obtained from a large sample, the study

did not employ a stratified sampling design. Additionally, while this study represents a unique and the largest survey conducted among French PE teachers, encompassing a substantial sample of 2,378 participants, this accounts for only 8% of the national PE teacher population. Consequently, caution should be considered when extrapolating our results, as it cannot be assumed that the studied cohort is fully representative of French PE teachers. Another limitation concerns the absence of contextual data, such as the geographical location of schools (urban versus rural) or socioeconomic environment. These factors could significantly influence the management of physical fitness in schools. Furthermore, the absence of official national training programs on the evaluation and development of students' muscular and cardiorespiratory fitness limits the possibilities for analyzing the effectiveness of existing interventions. Future research should integrate these variables to provide a more comprehensive understanding of their potential impact on physical fitness promotion in educational settings.

Conclusions

PE in schools offers a unique opportunity to enhance physical fitness and health in children and adolescents. However, findings from our study highlight several barriers within French schools, including insufficient training, structural constraints such as large class sizes and limited practice time, and low awareness of international recommendations regarding muscular strength. To maximize the impact of PE on public health, it is essential to: (*i*) prioritize the development of physical fitness in school curricula; (*ii*) strengthen initial teacher training and implement ongoing professional development programs focused on physical fitness assessment and effective interventions; (*iii*) improve teaching conditions (time, resources, class sample sizes); (*iv*) establish a national surveillance platform to monitor physical fitness among youth in the school environment. In addition, practical solutions should be promoted, such as integrating specific modules on muscular strength and fitness into teacher education, encouraging the use of free online platforms (*e.g.,* FitBack, ONAPS) for fitness assessment and reporting, and offering hands-on workshops as part of professional development. These actions are crucial to enhancing the role of PE teachers in promoting the physical fitness and health for our future generations of children and adolescents.

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Ethics approval

This study did not involve any intervention, and was conducted on a volunteer basis. In this context, written informed consent was not required according to French human research regulations. The answers provided by PE teachers were anonymous and confidential. This data collection was approved by the French National Commission of the Informatics Personal Data.

Consent to participate

Written, informed consent was obtained from the adolescents and the parents.

Consent for publication

NA.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

DM, FC and JV designed research; DM, FC and JV conducted research; DM and LB analysed data and performed statistical analysis; DM, LB and JV wrote the paper; JV had primary responsibility for final content. All authors read and approved the final manuscript

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HEALTH PROMOTION

A Snapshot Investigation on Assessment of Role of Dietary Diversity in Healthy Ageing among Elderly Living at Ahmedabad City, India

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Keywords

Activity of daily living • Dietary Diversity • Elderly • Healthy ageing

Summary

Background. *Dietary Diversity (DD) is one of the crucial determinants to address Healthy ageing among elderly people.*
Objectives. *To estimate prevalence with concerned determinants of Dietary Diversity, to assess intake-pattern of various nutrients and correlation of dietary diversity with healthy ageing among study participants.*
Methodology. *A cross-sectional study was conducted among 192 Elderly people (≥ 60 years of age) residing at Ahmedabad city, India, selected by two-stage Cluster sampling [As per Rapid Assessment Method for Older People (RAM-OP) survey sampling technique]. A pretested, semi-structured questionnaire including Socio-Demographic and Dietary-Diversity related details was utilised as survey-instrument. Healthy ageing was assessed with selected General Health status using two domains of total five; namely general Activity of Daily Living and Instrumental Activity of Daily Living (IADL) were applied to collect relevant data.*
Results. *Prevalence of Dietary-Diversity was 44.27% among study-participants. Various determinants such as living alone, socio-economic-class, co-morbidities, type of diet, oral health and meal-frequency revealed statistically significant association with Dietary Diversity. Cereals (96.9%), roots and tubers (91.7%), and condiments and mushrooms (90.1%) were the most common food-groups consumed by study participants. Of 85 participants with positive dietary diversity, more than two-thirds (67, 78.82%) were able to manage activities of daily living independently whereas approximately three-fifth (66, 61.68%) of sub-cohort of counterpart could manage the same independently. Predictors of IADL like use of telephone, practice of taking medications and managing their own money showed statistically significant association with presence of dietary-diversity.*
Conclusion. *Dietary diversity was prevalent among less than half of study-participants. A diverse diet showed statistical significant role in ensuring independence in general activities of daily living while gender-specific variations for instrumental activities of daily living.*

Introduction

The World Health Organisation (WHO) has defined "older people" as, those who are 60 years of age or older [1]. Population of elderly individuals is consistently growing in nations with advanced medical and social services and a high quality of life. By 2025, the global population of elderly individuals is projected to exceed 1.2 billion, with a significant majority residing in developing nations [2]. Based on the data from Census 2011, India is home to 104 million older individuals, accounting for 8.6% of the overall population [3]. The significant change in the proportion of older Indians presents a range of social, economic, and healthcare challenges that need to be addressed.
The food choices and eating practices of older individuals have a significant impact on their nutrient adequacy and overall health. The food choices of older individuals are influenced by a variety of factors, including ageing, psychosocial factors, personal resources, life experience, living situation, perceived health, personal motivation and support from other family members [4]. Age-concerned factors such as oral and dental health, diminished appetite, and limited physical capabilities are common determinant in shaping the prevailed physical health at any given point.
Dietary diversity (DD) is defined as the number of foods or food groups people consume during a given period [5]. Dietary diversity is an important aspect of maintaining good health and wellbeing, as no single food can provide all the essential nutrients needed [6]. The policy encompasses a wide range of food groups, including milk and milk products, cereals, roots, and tubers, fruits and vegetables, meats, eggs, and fish, legumes, nuts, and seeds, fats, sugars, and other groups [7]. Dietary diversity guarantees the probability of sufficient and diverse nutrients. There are several negative consequences associated with low/poor dietary diversity, including an elevated risk of cardiovascular disease, cognitive decline, muscle loss, frailty, depression, and limitations in daily activities, reduced quality of life, increased healthcare costs, and a higher likelihood of death. Dietary diversity is closely linked to energy intake adequacy, which is important for maintaining optimal body function. Along with energy intake, the protein-source food group is important for promoting muscle anabolism. Fruits and vegetables are packed with a wide range of beneficial phytonutrients

that play a crucial role in protecting against various non-communicable diseases. In addition, Dietary diversity has a strong correlation with the diversity and abundance of numerous beneficial gut microbiota, which contribute to overall health and well-being [8].

The healthy ageing concept is a very broad term which can be assessed by many tools, namely Cognitive functioning, Physical functional status, chronic diseases, Personal disability and Instrumental disability. Activity of Daily Living (ADL) are self-care activities that a person performs daily (*e.g.,* eating, dressing, bathing, transferring between the bed and a chair, using the toilet, controlling bladder and bowel functions) [9]. Instrumental (IADL) are activities that are needed to live independently (*e.g.,* doing housework, preparing meals, taking medications properly, managing finances, using a telephone) [9].

Dietary diversity plays a significant role in the overall health and functional ability of elderly individuals, particularly in their ability to perform Activities of Daily Living (ADLs) and Instrumental Activity of Daily Living (IADL). ADLs are basic self-care tasks, including bathing, dressing, eating, toileting, and mobility whereas managing medications or planning meals, shopping or house cleaning are examples of IADL. IADLs require strong cognitive abilities. Deficiencies in nutrients like protein, calcium, vitamin D, and B vitamins have been linked to sarcopenia, osteoporosis, and cognitive decline, all of which can impair ADL and IADL. Nutrients such as omega-3 fatty acids, antioxidants (vitamins C and E), and polyphenols found in fruits, vegetables, nuts, and fish have neuroprotective effects [10]. Mental health is a key determinant of IADL performance. Depression, anxiety, or apathy can reduce the motivation and capacity to perform complex tasks. Dietary diversity, especially the inclusion of mood-enhancing nutrients like tryptophan, magnesium, and omega-3 fatty acids, supports emotional well-being [11].

Indian subcontinent, being in rapid transitional phase of demography, is bearing privileges and encumbrances of demographic dividend and burden respectively. To decrease liability for later cohort, direct out-of-pocket expenses arising out of adverse health and consequent multiple indirect expenses, healthy ageing is utmost important. Geriatric health is often disregarded in India due to socio-cultural customs and beliefs. The key health programs of government are either directed towards maternal and child health or communicable disease. The emerging status of global hub of NCDs has not yet claimed sufficient health-budget in total amount, planned routinely by health system. As a short-term solution the NCDs related program is fitting the square pegs in round holes. Dietary diversity can work as effective primordial and primary prevention tool against majority of NCDs in true sense. To assess the spectrum of dietary diversity, considering the resources available with investigators, current research was planned at one of the biggest cities of western India, *i.e.,* Ahmedabad, which is financial capital of Gujarat province and situated at central part of state with benefit of very well connectivity to all intra-state and inter-state destinations by various means of travelling across country. It typically presents example of ever-evolving urban-setting where migrants from almost all parts of India are settling due to city's exponential growth in industrial and other sectors. The young generations settled recently is having fusion cultural pattern which includes varied dietary pattern whereas their dependents of extreme ages prefer their cultural diet in recent years of migration.

Current study was conducted with objectives of: 1) To estimate prevalence of Dietary Diversity among study participants; 2) To evaluate various determinants associated with Dietary Diversity; 3) To describe presence of intake pattern of various Dietary nutrients among study participants; 4) To find correlation between Dietary Diversity and selected General Health status among study participants.

Methods

A cross-sectional study (snapshot investigation) was conducted from February to June 2024 among community-dweller elderly people (≥60 years of age) [1] who were residing at Ahmedabad city, India. The sample-size was calculated as per guidelines from Rapid Assessment Method-Older People (RAM-OP) survey [7]. Accordingly, calculated sample-size of 192 was considered for current study. Sampling-frame was constituted by all elderly people residing at administrative territory of Ahmedabad Municipal Corporation. For further sampling technique, Two-stage cluster sampling method [7] was used as per the RAM-OP survey guidance.

Ahmedabad city is divided into seven administrative zones by the Municipal Corporation Authority [12]. Considering resource limitations, four of these zones were selected randomly by lottery method in first stage of sampling. Each zone is divided in multiple wards for administrative ease by municipal corporation. From each selected zone, four wards were selected by a table of random numbers. So, total (4 zones) x (4 wards from each zone) = 16 wards (study area) were included in final sampling frame for current research. In second stage of sampling; the list of households was obtained from respective ward offices of municipal corporation. From each selected ward, 12 households were selected by systematic random sampling with K^{th} sampling interval. (Total 16 wards X 12 households per ward = 192 households were selected). Each selected ward had a different sampling interval, *i.e.,* K^{th} number, as each ward was having a unique number of registered households in its list. The first household of pre-selected ward was chosen randomly with the currency note method, and remaining eleven households were selected subsequently by adding the K^{th} number applicable to that ward.

From each selected households, one elder person was recruited as study participant who fulfils inclusion criteria. If, there were more than one elder person in selected household available at the time of visit who fulfilled the inclusion criteria, then only one

participant was selected by the lottery (chit) method. A selected participant was interviewed personally after receiving oral informed consent. If no elder participant was available in selected household, then the next immediate numbered household was approached. The same sampling technique was applied to all sixteen pre-selected wards to collect data from twelve elderly persons from twelve households. Thus, 16 X 12=192 in toto participants were recruited.

Elderly participants, who were willing to participate, prepared to give oral informed consent, were pre-considered inclusion criteria while migrants (non-residents as per voter list of Municipal Corporation); debilitated elderly people who were severely ill to respond the questionnaire including hearing and/or mental disability were excluded.

Draft questionnaire was pilot tested with a sample of twenty elderly respondents in the field practice area of Urban Health Teaching Centre of Mother Institute. These responses were excluded from final data analysis. A pretested, pre-validated, semi-structured questionnaire was used to collect the relevant details which were filled out by interviewer in manual forms. Questionnaire encompasses socio-demographic information such as age, gender, occupation, and income, as well as personal details like habits, diet and oral health, anthropometric details such as height, weight, and body mass index (BMI) according to the Asia Pacific classification [13]. It also collected Dietary Diversity-related details using the RAM-OP standard questionnaire format, [7] which includes 11 questions for 11 food-groups and meal frequency using the 24-hour recall method. For dietary diversity assessment; participants who had taken ≥ 6 food groups and <6 food groups were considered dietary-diversity present and diversity absent, respectively. Socio-economic class was assessed by Modified Kuppuswami classification as per January 2024 update [14].

Healthy ageing is about creating the environments and opportunities that enable people to be and do what they value throughout their lives. Being free of disease or infirmity is not a requirement for healthy ageing, as many older adults have one or more health conditions that, when well controlled, have little influence on their wellbeing [15]. Healthy Ageing assessment includes 5 domains: (i) Cognitive functioning, (ii) Physical functional status, (iii) Chronic diseases, (iv) Personal disability and (v) Instrumental disability. Out of these five domains, on account of time and technical constrains, healthy ageing status was assessed using last two domains after feasibility check during pilot study. Domain of "personal disability" was assessed by Activity of Daily Living (ADL) questionnaire which included 6 questions – each having equal scoring value, 0 for dependent and 1 for independent; final score value range 0-6, where participants with total scores of 6 and <6 were considered independent and dependent, respectively [16]. Personal disability was considered when there is impairment in at least one ADL (bathing, dressing, toileting, transferring, and eating) [17]. Second domain of "instrumental disability" was assessed by Instrumental Activity of Daily Living (IADL) questionnaire which included six questions for male participants and nine questions for female participants [8, 18]. Each question had three categories; namely unable to perform independently, need assistance to perform and perform independently with score value of 1, 2 and 3 respectively [16].

Both, ADL and IADL questionnaire are pre-validated and the same was re-confirmed in pilot study during current research. Data were analysed using IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. and MS Excel 2021, applying appropriate statistical tests. For descriptive statistics- mean, standard deviation and proportion; for continuous variables- unpaired t-test and ANOVA were applied. Association between dietary diversity with components of ADL and IADL were analysed by applying unpaired-t test and chi-square test respectively. Logistic regression using odds ratio was applied to evaluate the risk conditions that are associated with an unvaried diet. The research was approved by Institutional Ethical Committee vide its letter no. GCSMC/EC/Research Project/Approve/2024/618.

Results

Among 192 study participants, 85 (44.27%) showed presence of Dietary Diversity (Score ≥ 6) while 107 (55.73%) participants revealed lack of Dietary Diversity (Score <6). Thus, Prevalence of Dietary Diversity was found to be 44.27% among study participants. In context to gender-specific prevalence, of total 94 male participants, 46 (48.9%) and of total 98 female participants, 39 (39.79%) had dietary diversity present showing favourable results amongst male gender.

Of total recruited participants, the age-distribution of studied elderly was near-equally distributed among 60-70 (73, 38.02%), 70-80 (61, 31.77%) and more than 80 (58, 30.20%) years sub-groups with slightly more preponderance of 60-70 years age-group. The distribution of dietary diversity in these three sub-groups showed diverse prevalence with maximum revelation in 70-80 years age-group, *i.e.,* 50.82% while minimal presence in first decade of geriatric phase of life, *i.e.,* 60-70 years (39.73%). The gender distribution of recruited participants was almost equal, 94 (48.96%) males and 98 (51.04%) females. Nearly half of studied male participants (46, 48.94%) while two-fifth of recruited females (39, 39.80%) showed presence of dietary diversity in their food. The revealed gender difference for prevalence of dietary diversity did not establish statistical significance. ($p = 0.204$). Of total participants surveyed, majority (102, 53.13%) had lost their spouse while nearly one-third, (68, 35.42%) were living with spouse whereas 38 (19.79%) participants were living alone, irrespective of spouse alive or not. Almost two-thirds of elderly (134, 69.79%) were suffering from one or more co-morbidities at the time of interview. The presence of dietary diversity was statistically significantly affected by living alone and suffering from co-morbidities. Majority of elderly belonged to class III and IV of modified Kuppuswamy

classification, which had statistically significant impact on presence of dietary diversity. In context of BMI, 134 (69.76%) elderly participants were in normal category of Asia-pacific classification whereas 52 (27.08%) were in pre-obese category. Types of diet consumed (vegetarian, eggetarian and mixed variety) revealed statistically significant impact on presence of dietary diversity. Two-fifths (80, 41.67%) of participants were addicted to one or more substances, mainly tobacco and majority (176, 91.67%) had habit of drinking tea/coffee more than once a day. The dentin status and meal frequency per day were assessed which revealed strong statistical significance ($p < 0.0001$ and 0.0005 respectively) on presence of dietary diversity amongst studied elderly.

A value of Odd's Ratio (OR) >1 suggests higher odds with *lack* of dietary diversity (*i.e.,* negative outcome), and OR < 1 suggests protective effect or higher odds with dietary diversity (*i.e.,* positive outcome). The reference group (OR = 1) is the category against which others were compared. Females had 1.45 times higher odds of *not* having dietary diversity than males. Divorced status had 2.11 times higher odds of not having dietary diversity than married participants. Participants with class IV socio-economic status had 3 times whereas participants representative from class V socio-economic strata had 3.67 times higher odds of lacking dietary diversity as compared to participants from class II. Individuals with mixed diet had 0.26 times lower odds of lacking dietary diversity than participants with vegetarian diet. Edentulous participants had 21.6 times while partially dentulous had 5.2 times higher odds of lacking dietary diversity than dentulous participants. Participants who were having 4-6 meals in a day were having 0.29 times lower odds of lacking dietary diversity than those who were having 1-3 meals in a day. (Tab. I).

As described in methodology, the dietary information to classify dietary diversity was collected by asking intake of 11 sub-groups of food as pre-defined in RAM-OP standard questionnaire format [7]. The result revealed cereals (186, 96.9%), roots and tubers (176, 91.7%), and condiments and mushrooms (173, 90.1%) were the most common food-groups consumed by more than 90% of study participants. All meats (34, 17.7%), fish (31, 16.1%) and eggs (79, 41.1%) were the least consumed food-groups. (Fig. 1).

The activity of daily living was assessed as a component of healthy ageing. The association of same with dietary diversity was found statistically significant. Of 85 elderly with dietary diversity present in their diet, more than two-thirds (67, 78.82%) were able to manage activities of daily living independently whereas approximately three-fifth (66, 61.68%) of sub-cohort with dietary diversity absence in diet could manage the same independently. (Tab. II).

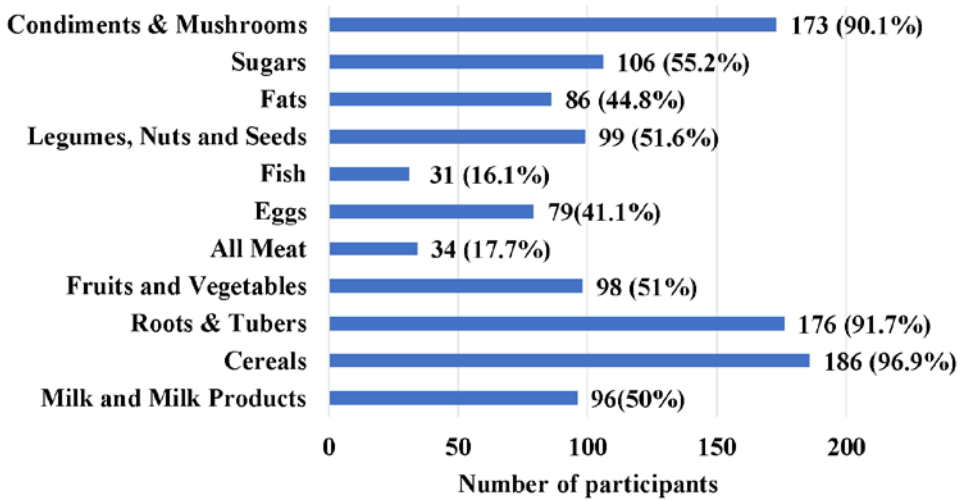
The effect of presence of dietary diversity on instrumental activities of daily living (IADL) was assessed with six and nine questions in male and female gender respectively. The three common variables, namely use of telephone, practice of taking medications and managing their own money showed statistically significant association with dietary diversity. The participants with female gender showed statistically significant association with dietary diversity in five additional variables than mentioned above. Getting to places which are out of walking distance, preference/attitude to take medication by self, shopping for groceries, preparing their own meals and doing their own housework were instrumental activities of daily living which were significantly associated with dietary diversity amongst female elderly participants. (Tab. III).

Discussion

The study aimed to evaluate the prevalence and determinants of dietary diversity among older adults and its association with various aspects of health and daily living. Review of literature at renowned medical databases did not reveal much information about assessment of Dietary Diversity among Elderly using RAM-OP questionnaire, especially in Indian sub-continent.

The prevalence of Dietary Diversity in current research was found to be 44.27% while similar research conducted

Fig. 1. Intake pattern of various Food-groups among study participants (n = 192).



Tab. I. Association of various socio-demographic, anthropometric and diet related determinants with Dietary Diversity (n = 192).

Variables	Dietary Diversity		Total	Mean	SD	Odds ratio (95% CI)	*p* Value
	Present (n = 85)	Absent (n = 107)					
Age (In Completed Years)							
60-70	29 (39.73%)	44 (60.27%)	73	0.40	0.49	1	**0.431#**
70-80	31 (50.82%)	30 (49.18%)	61	0.51	0.50	0.64 (0.32-1.27)	
> 80	25 (43.10%)	33 (56.89%)	58	0.43	0.50	0.87 (0.43-1.75)	
Gender							
Male	46 (48.94%)	48 (51.06%)	94	0.49	0.50	1	**0.204***
Female	39 (39.80%)	59 (60.20%)	98	0.40	0.49	1.45 (0.82-2.57)	
Marital Status							
Married	38 (55.88%)	30 (44.11%)	68	0.56	0.50	1	**0.08#**
Widow	40 (39.22%)	62 (60.78%)	102	0.39	0.49	1.96 (1.05-3.66)	
Divorced	6 (37.50%)	10 (62.5%)	16	0.37	0.50	2.11 (0.69-6.47)	
Living together	1 (50%)	01 (50%)	02	0.50	0.70	1.27 (0.08-21.1)	
Single (Never married)	0 (0.00%)	04 (100%)	04	0.00	0.00	-	
Living Alone							
Yes	9 (23.68%)	29 (76.31%)	38	0.24	0.43	1	**0.004***
No	76 (49.35%)	78 (50.64%)	154	0.49	0.50	1.38 (0.78-2.45)	
Any Co-Morbidities present							
Yes	68 (50.75%)	66 (49.25%)	134	0.49	0.50	1	**0.001#**
No	7 (50%)	07 (50%)	14	0.50	0.51	1.03 (0.34-3.1)	
Don't know	1 (16.67%)	05 (83.33%)	06	0.08	0.28	5.15 (0.59-45.28)	
Socio-Economic Status$							
Class I	2 (100%)	00 (0.00%)	02	1.00	0.00	-	**0.003#**
Class II	22 (59.46%)	15 (40.54%)	37	0.59	0.50	1	
Class III	30 (55.56%)	24 (44.44%)	54	0.56	0.50	1.17 (0.5-2.74)	
Class IV	21 (32.81%)	43 (67.18%)	64	0.33	0.47	3 (1.3-6.95)	
Class V	10 (28.57%)	25 (71.42%)	35	0.29	0.46	3.67 (1.37-9.81)	
Type of Family							
Joint	33 (49.25%)	34 (50.75%)	67	0.49	0.50	1	**0.308***
Nuclear	52 (41.6%)	73 (58.4%)	125	0.42	0.49	1.36 (0.75-2.47)	
Body Mass Index (BMI)¥							
Underweight	0 (0.00%)	01 (100%)	01	0.00	0.00	-	**0.89 #**
Normal	57 (42.54%)	77 (57.46%)	134	0.43	0.50	1	
Pre-Obese	26 (50%)	26 (50%)	52	0.50	0.51	0.74 (0.39-1.41)	
Obese class-1	2 (40%)	03 (60%)	05	0.40	0.55	1.11 (0.18-6.86)	
Obese class-2	0 (0.00%)	00 (0.00%)	00	0.00	0.00	-	
Obese class-3	0 (0.00%)	00 (0.00%)	00	0.00	0.00	-	
Type of Diet							
Vegetarian	39 (36.45%)	68 (63.55%)	107	0.36	0.48	1	**0.004 #**
Eggetarian	22 (51.28%)	28 (48.71%)	50	0.44	0.50	0.73 (0.37-1.28)	
Mix	24 (77.78%)	11 (22.22%)	35	0.69	0.47	0.26 (0.12-0.59)	
Habit of tea/coffee							
Yes	78 (44.32%)	98 (55.68%)	176	0.44	0.50	1	**0.967***
No	7 (43.75%)	9 (56.25%)	16	0.44	0.51	1.02 (0.36-2.87)	
Addiction							
Yes	40 (50%)	40 (50%)	80	0.50	0.50	1	**0.180***
No	45 (40.18%)	67 (59.82%)	112	0.40	0.49	1.49 (0.83-2.66)	
Oral Health (Teeth)							
Dentulous	36 (70.59%)	15 (29.41%)	51	0.71	0.46	1	**<0.0001#**
Partially Dentulous	30 (31.57%)	65 (68.42%)	95	0.32	0.47	5.2 (2.48-10.92)	
Edentulous	1 (10%)	09 (90%)	10	0.10	0.32	21.6 (2.51-185.8)	
Artificial Denture	18 (50%)	18 (50%)	36	0.50	0.51	2.4 (0.99-5.84)	
Meal Frequency/day							
1-3	56 (37.58%)	93 (62.42%)	149	0.38	0.49	1	**0.0005***
4-6	29 (67.44%)	14 (32.56%)	43	0.67	0.47	0.29 (0.14-0.6)	

* Un-paired t test; # ANOVA test; $ Modified Kuppuswami classification (As per January 2024 update); ¥ Asia-pacific classification.

Tab. II. Association between Dietary Diversity and Activity of Daily Living (n = 192).

Selected General Health Status Variable	Dietary Diversity		Mean	SD	*p* Value (un-paired t test)
	Present n (%)	Absent n (%)			
ADL (Activity of Daily Living)					**0.01**
Independent	67 (78.82)	66 (61.68)	0.50	0.50	
Dependent	18 (21.18)	41 (38.32)	0.31	0.46	
Total	85 (100)	107 (100)	--	--	

Tab. III. Association between Instrumental Activity of Daily Living (IADL) and Dietary Diversity (DD) among study participants.

IADL Variables	Categories#	DD in Males (n = 94)			*p* Value	DD in females (n = 98)			*p* Value
		Present	Absent	Total		Present	Absent	Total	
Can you use the telephone?	I	13 (31.71%)	28 (68.29%)	41	**6.47 (0.01)**	11 (20.75%)	42 (79.25%)	53	**18.603 (<0.0001)**
	II	25 (59.52%)	17 (40.48%)	42		21 (58.33%)	15 (41.67%)	36	
	III	8 (72.72%)	3 (27.27%)	11		7 (77.78%)	2 (22.22%)	9	
Can you get to places that are out of walking distance?	I	12 (38.71%)	19 (61.29%)	31	2.07 (0.36)	7 (20%)	28 (80%)	35	**10.33 (0.006)**
	II	18 (56.25%)	14 (43.75%)	32		24 (55.81%)	19 (44.19%)	43	
	III	16 (51.64%)	15 (48.39%)	31		8 (40%)	12 (60%)	20	
Can you go shopping for groceries?	I	14 (38.89%)	22 (61.11%)	36	2.63 (0.27)	9 (24.32%)	28 (75.68%)	37	**5.95 (0.05)**
	II	17 (58.62%)	12 (41.37%)	29		19 (48.72%)	20 (51.28%)	39	
	III	15 (51.72%)	14 (48.28%)	29		11 (50%)	11 (50%)	22	
If you had to take medication, could you do it? (males, n=74) (females, n=73)	I	5 (31.25%)	11 (68.75%)	16	5.04 (0.08)	2 (20%)	8 (80%)	10	**8.21 (0.01)**
	II	24 (60%)	16 (40%)	40		18 (42.86%)	24 (57.14%)	42	
	III	12 (66.67%)	6 (33.33%)	18		15 (71.42%)	6 (28.57%)	21	
Do you take your own medication? (males, n=20) (females, n=25)	I	0 (0.00%)	5 (100%)	5	**15.15 (0.001)**	0 (0.00%)	7 (100%)	7	**18.06 (<0.0001)**
	II	1 (9.09%)	10 (90.91%)	11		1 (6.67%)	14 (93.33%)	15	
	III	4 (100%)	0 (0.00%)	4		3 (100%)	0 (0.00%)	3	
Can you manage your own money?	I	6 (24%)	19 (76%)	25	**8.48 (0.01)**	7 (6.66%)	23 (76.66%)	30	**5.67 (0.05)**
	II	21 (58.33%)	15 (41.66%)	36		19 (43.18%)	25 (56.81%)	44	
	III	19 (57.57%)	14 (42.42%)	33		13 (54.16%)	11 (45.83%)	24	
Can you prepare your own meals? *	I	-	-	-	-	7 (23.33%)	23 (76.66%)	30	**7.85 (0.02)**
	II	-	-	-		13 (37.14%)	22 (62.86%)	35	
	III	-	-	-		19 (57.57%)	14 (42.42%)	33	
Can you do your own housework? *	I	-	-	-	-	16 (43.24%)	21 (56.76%)	37	**3.62 (0.04)**
	II	-	-	-		16 (53.33%)	14 (46.67%)	30	
	III	-	-	-		12 (30.77%)	27 (69.23%)	39	
Can you do your own laundry? *	I	-	-	-	-	14 (41.18%)	20 (58.82%)	34	0.74 (0.23)
	II	-	-	-		13 (52%)	12 (48%)	25	
	III	-	-	-		16 (43.24%)	21 (56.76%)	37	

*As per described in methodology; In IADL assessment, Male participants had 6 questions while Female participants had 9 questions. Classification of IADL categories: I – Unable to perform independently or even with assistance, II - Unable to perform independently, need assistance to perform, III – able to perform independently

by Bayih et al. [19] at Ethiopia revealed the same as 54.5% which is quite near to finding of current study. A few research evaluated dietary diversity with Dietary Diversity Severity (DDS) score (cut-off level = 20) [8, 20], like Chalobol C. [8] at Thailand and Rathnayake et al. [20] at Sri Lanka, following this evaluation technique, revealed the mean (SE) score of DDS as 18.4 and 11.4 respectively. Both of these research revealed diverse finding, may be due to difference in socio-economic and cultural diversity of both countries.

In current study, Various Socio-demographic, Anthropometric and Diet related variables like-Living alone, comorbidities, socio-economic class, and type of diet, oral health and meal frequency were found to have statistically significant association with Dietary Diversity. A significant portion of the study participants were widowed (53.1%) and lived with comorbidities (80%). These factors can influence dietary choices and access to diverse food options. Shahar et al [21] assessed weight change from baseline and following widowhood, dietary intake, eating behavior, depression, and cognitive and physical functioning revealed widowed people were

found to be at increased risk for weight loss due to decreased appetite and enjoyment of their meals. Hanna and Collins [22] in their study found that living alone was negatively associated with dietary diversity.

In current research, the socio-economic status found statistically significant association with Dietary Diversity where majority of participants who lacked dietary-diversity belonged to lower socio-economic class. Sobal J. et al. [23] suggested that with lower socio-economic status often associated with reduced dietary diversity due to financial constraints and limited access to a variety of foods which is in line with current findings.

In current study, Types of diet consumed and meal frequency per day revealed statistically significant impact on presence of dietary diversity; the same findings were found reiterated in results revealed by Ruel MT [24] reflecting the importance of dietary variety and regular meal patterns. The association of dietary-diversity with oral health is particularly noteworthy. Participants with better oral health (dentulous) showed positive dietary diversity. The same is supported by findings of Logan et al. [25] concluding that having ≥21 natural remaining teeth positively affected the future intake of fruit, vegetables, and nuts, as well as diet quality, thus influencing dietary diversity.

A significant correlation between dietary diversity and various components of ADL and IADL was one of findings of current research. It was revealed that out of 85 participants with positive dietary diversity, more than two-thirds were able to manage activities of daily living independently whereas approximately three-fifth of sub-cohort of counterpart could manage the same independently. These findings were supported by Hsiao et al. [26] and Zhu et al. [27] in their research which linked dietary diversity with better functional status and quality of life in older adults.

The significant association was found among female participants regarding IADL, such as the ability to prepare meals and manage money, suggest that dietary diversity may have gender specific concerns on functional capabilities. A study conducted by Carmona et al. [28] reported that female gender was found to be associated with disability in general; whereas more individuals had disability for instrumental activities of daily living than disability for basic activities of daily living.

In current research, the elderly population in Ahmedabad, a typical exemplary ever-evolving urban city of western India, displayed a high intake of cereals and tubers but notably lower consumption of fish and meat. India has a vast geographical diversity, dietary patterns vary significantly across regions. Residents of coastal states like Kerala in southern India and West Bengal at north-eastern part of country prefer diets rich in seafood, coconut, and rice due to proximity to the sea and tropical agro-climatic conditions [29, 30]. The residents of northern plains focus more on wheat, dairy, and pulses, reflecting agrarian lifestyles and cultural practices [31]. Mountainous and tribal regions, such as those in the far northeast and central India, often rely on fermented foods, coarse grains like millets, and locally foraged greens, shaped by indigenous food systems and terrain-based access [32, 33]. These regional contrasts suggest that geography and availability of foods significantly influence dietary diversity.

Conclusion

Positive Dietary Diversity was observed amongst less than half of studied elderly. Various determinants like-status of living alone or with family, presence of any co-morbidities, socio-economic-class, type of diet, oral-health and meal frequency revealed statistically significant association with Dietary Diversity. In majority of the participants, cereals, Roots & Tubers, Condiments and mushrooms, Sugars, Legumes, Nuts, Seeds, fruits and vegetables were included in the Diet. Independence in general activities of daily living was statistically significantly associated with Dietary Diversity while the IADL showed gender-specific varied association with dietary-diversity.

Recommendation

Considering resource-limited setting in India, targeted nutrition interventions for elderly individuals living alone or with low socioeconomic status to improve dietary diversity can be planned. Healthcare providers should optimally utilize opportunistic screening in terms of assessment and promoting balanced diets during routine visits; considering factors like age, oral health, living with family or alone, Socio-economic status, type of diet etc. while advising diet. Community-based programs and caregiver support can enhance dietary diversity, ensuring independence in daily activities. Policymakers should prioritize nutrition education and resources for vulnerable elderly populations while facing demographic transition.

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Conflict of interest statement

The researcher(s) claim(s) no conflicts of interest.

Authors' contributions

VRD, KAP: conceptualization, methodology, study design, review of literature, data entry and analysis, writing–original draft, writing-review & editing. KAP: data Collection.

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HEALTH PROMOTION

Comparing vape use and perceptions among pharmacy and non-pharmacy students from two universities in the US and UK

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Keywords

Vape • E-Cigarette • Electronic Nicotine Delivery System • University Students, Pharmacy

Summary

Introduction. *Little research exists regarding pharmacy student vaping habits or differences among students from different countries.*
Methods. *A novel 19-item questionnaire was distributed in November 2023 to students at The University of Bath (United Kingdom) and The University of Texas at Austin (United States) to compare vape use and perceptions among pharmacy and non-pharmacy students from the two universities. All pharmacy students at both institutions were invited to complete the survey. A non-pharmacy student control group was identified through snowball sampling (i.e., the survey was distributed to a convenience sample of non-pharmacy students at each school, asking them to complete and distribute to peers). To incentivize participation, one respondent received a $100 reward. Data was analyzed using descriptive statistics. Chi-square and Wilcoxon Rank Sum tests were used to compare answers between pharmacy and non-pharmacy and UK and US participants. A p-value < 0.05 was deemed significant.*
Results. *Overall, 372 students completed the survey (25% pharmacy student response rate). Vape use significantly differed between pharmacy and non-pharmacy students ($p = 0.03$). Among 212 pharmacy students, 49% reported vape ever-use versus 59% of the 158 non-pharmacy students. Significant differences were found in harm perceptions; more pharmacy students believed vapes are cancer-causing, affect the health of others nearby, should be banned in public, and are ineffective for quitting cigarettes. Few differences were observed between UK and US students.*
Conclusion. *Pharmacy students were less likely to vape and exhibited heightened awareness of associated risks than non-pharmacy students. Few differences were observed between UK and US students surveyed.*

Introduction

Vapes, also commonly referred to as vape pens, electronic cigarettes or e-cigarettes, were introduced around 2005, and originally marketed as a safer alternative to help smokers reduce or quit smoking traditional tobacco cigarettes and decrease smoking-related health consequences [1]. Smoking tobacco cigarettes continues to be the largest avoidable cause of death and serious disability in most developed countries, including the United States of America (US) and United Kingdom (UK) [2, 3]. Vapes do not contain tobacco nor do they produce smoke from combustion, the source of the majority of toxic, cancer-causing chemicals, and therefore are believed to be less harmful than regular tobacco cigarettes. However, this does not mean that they are harmless [4]. Vapes contain a variety of chemicals (*e.g.,* preservatives, flavorings, and heavy metals) that may be carcinogenic and contribute to lung disease, and typically contain nicotine, which confers considerable addiction potential, increases the risk of cardiovascular disease and may cause fetal harm when used during pregnancy [1, 4, 5]. There is also concern that vaping among adolescents and young adults may have negative impacts on the developing brain, confer seizure risk, and serve as a gateway to future cigarette smoking and reverse decades of progress in reducing national tobacco use rates [4, 6, 7]. It is unlikely that all of the long-term risks and health consequences have been established, since they have been around for less than 20 years [8].

Vape popularity has surged in the past decade, particularly in adolescents and young adults [9, 10]. In 2021, people between ages 18-24 years were the most likely US adults to vape, with a current use rate of 11% [11]. While there has been increasing research into vape use among teenagers, university students and young adults, research focusing specifically on healthcare students is limited, particularly pharmacy students. Franks and colleagues identified that 44% of healthcare professional students believed vapes to be less harmful than traditional cigarettes [12], while Sahr and colleagues found pharmacy students to have a more negative perception regarding vapes than other health care students, with less pharmacy students willing to recommend vapes as a smoking cessation tool [13]. Furthermore, the few studies assessing pharmacy student vape use and perceptions have been small studies in

single locations. Surveying students across multiple universities and countries allows results to be more generalizable to a wider population and explore whether cultural differences may affect vape use and perceptions. This study was conducted to compare vape use and perceptions among pharmacy and non-pharmacy students from two universities; one in the United Kingdom (UK) and the other in United States (US). Given the important role pharmacists play in tobacco use disorder treatment and the potential harms of e-cigarettes, understanding pharmacy students' vape use and perceptions regarding their benefits and harms is important for public health. This information can help guide pharmacy educators' efforts to ensure pharmacy students are well-informed regarding their own health decisions and prepared to educate patients regarding vaping.

Methods

Instrument

A novel, literature informed [12, 13], 19-item survey regarding vape use and perceptions was created by a pharmacy student from the University of Bath (UK) and faculty member from The University of Texas at Austin College of Pharmacy, as part of a study abroad program. The survey was disseminated electronically using Qualtrics® (Provo, UT) to pharmacy and non-pharmacy students from both universities. Prior to distribution, pilot testing was conducted with students across different courses at both universities, with revisions made to improve the clarity, based on student feedback. The study was ethically approved by both The University of Bath and The University of Texas at Austin's institutional review boards.

In addition to demographics, the survey consisted of: multiple choice questions regarding personal use history of vapes, tobacco, alcohol and cannabis; select all that apply questions (with optional free response) regarding perceived or personal motivations and deterrents for vaping (vape ever users were asked what their main motivation to vape was and vape never users were asked what they believed were the most common motivations for other people to vape; vape non-users were also asked what had deterred them from vaping); 'Yes, no, or unsure' questions regarding perceived harms (*e.g.,* whether they believe vapes contain cancer-causing ingredients, whether exhaled vapor can negatively impact the health of other people, and whether they believe that vaping should be banned in public places) and whether they perceive vapes to be an effective smoking cessation method; and Likert scale questions comparing the harm, addictive potential, and ease of quitting vapes versus traditional cigarettes. Display logic was incorporated to variably ask follow-up questions depending on student's responses to previous questions (*e.g.,* only those who currently vape were asked about their vaping frequency). The survey took approximately 5-10 minutes to complete.

Distribution

In November 2023, the anonymous, voluntary survey was distributed via email to all pharmacy students currently enrolled at The University of Bath in the UK and The University of Texas at Austin in the US. The survey included an information sheet and consent form for participants to read and confirm acceptance prior to beginning. Recruitment differed for non-pharmacy students because the investigators did not have a means to feasibly distribute the survey to all non-pharmacy students at each university. Snowball sampling methodology was implemented to obtain the non-pharmacy student sample, with the lead investigator disseminating the survey to personal contacts at both universities, asking participants to complete the survey and share it with peers from their university. Additionally, QR codes linking to the survey were distributed to students around campus at The University of Texas at Austin, and an email invitation was sent to all students studying within the Life Sciences department at The University of Bath. Finally, the lead investigator posted a link on social media, directing students studying at either university to fill out the questionnaire. The questionnaire was open for three full weeks and closed in December 2023.

To incentivize participation, students completing the survey could enter a drawing for a single $100 gift card. Participation in the prize draw was optional and required students to complete a separate form after the survey, which was not linked to their responses, guaranteeing anonymity. Engagement in the prize draw was optional.

Statistical Analysis

Data was analyzed using descriptive statistics. Counts and percentages were used for categorical data and median and interquartile range for numerical data because they were not normally distributed, as determined by the Shapiro-Wilk and Anderson-Darling tests. Chi-square and Wilcoxon Rank Sum tests were used to compare answers between pharmacy and non-pharmacy students, as well as UK and US participants. A p-value of < 0.05 was deemed a statistically significant difference.

Results

Pharmacy student response rates were 27% (110/411) at The University of Bath and 24% (101/420) at The University of Texas at Austin. One additional pharmacy student completed the survey but did not indicate which school they attended so they were included in pharmacy vs non pharmacy comparisons but not country comparisons. Given the various methods employed to recruit non-pharmacy students, an unknown number of individuals were approached, and the response rate could not be calculated. In total, 372 students completed the survey; 30% (n = 114/372) were male, 68% (n = 258/372) were female and 2% (n = 6/372) were non-binary. Median age was 21 years. There was a relatively even distribution among groups, with a small majority from the UK (58%)

Tab. I. Demographics and vaping and substance use habits.

Characteristic	Pharmacy n (%)	Non-pharmacy n (%)	P value	UK n (%)	US n (%)	P value
Age (years)			**< 0.01**			**< 0.01**
Median	22	21		20	24	
IQ range	19-25	19-22		19-21	22-25	
Gender			0.17			0.22
Female	152/212(72)	99/158(63)		145/216(67)	109/156(70)	
Male	57/212(27)	57/158(36)		67/216(31)	47/156(30)	
Non-binary/Third gender	3/212(1)	2/158(1)		4/216(2)	0/156(0)	
Have you ever used traditional cigarettes or other forms of tobacco?			**< 0.01**			0.79
Never used	151/209(72)	74/157(47)		130/215(61)	97/152(64)	
Occasional use in the past	39/209(19)	45/157(29)		51/215(24)	33/152(22)	
Regular use in the past	8/209(4)	9/157 (6)		12/215(6)	5/152(3)	
Occasional use currently	8/209(4)	26/157(17)		18/215(8)	15/152(10)	
Regular use currently	3/209(1)	3/157(2)		4/215(2)	2/152(1)	
Have you ever drunk alcohol?			**< 0.01**			0.06
Never	19/209(9)	12/157(8)		25/215(12)	5/152(3)	
Less than once a month	50/209(24)	12/157(8)		34/215(16)	29/152(19)	
Once a month	44/209(21)	29/157(18)		39/215(18)	35/152(23)	
Once a week	61/209(29)	60/157(38)		75/215(35)	46/152(30)	
Several times a week	34/209(16)	43/157(27)		41/215(19)	36/152(24)	
Daily	1/209(1)	1/157(1)		1/215(<1)	1/152(1)	
Have you ever used cannabis?			**0.01**			**< 0.01**
Never	126/208(61)	75/157(48)		131/214(61)	71/152(47)	
Occasional use in the past	63/208(30)	47/157(30)		61/214(29)	49/152(32)	
Regular use in the past	4/208(2)	11/157(7)		10/214(5)	5/152(3)	
Occasional use currently	12/208(6)	21/157(13)		11/214(5)	22/152(14)	
Regular use currently	3/208(1)	3/157(2)		1/214(1)	5/152(3)	
Do you vape?			**0.03**			0.07
Never	107/209(51)	65/157(41)		103/215(48)	71/152(47)	
Occasional use in the past	67/209(32)	44/157 (28)		64/215(30)	46/152(30)	
Regular use in the past	10/209(5)	17/157 (11)		21/215(10)	6/152(4)	
Occasional use currently	16/209(8)	18/157 (12)		19/215(9)	15/152(10)	
Regular use currently	9/209(4)	13/157 (8)		8/215(3)	14/152(9)	
If you vape currently, how often do you vape?			**0.90**			0.81
Less than once a month	0/25(0)	1/31(3)		1/27(3)	0/29(0)	
Once a month	3/25(12)	4/31(13)		4/27(15)	3/29(10)	
Once a week	8/25(32)	8/31(26)		8/27(30)	8/29(28)	
Several times a week	5/25(20)	7/31(23)		5/27(19)	7/29(24)	
Daily	9/25(36)	11/31(35)		9/27(33)	11/29(38)	

Demographics and substance use history by area of study and university location. US: United States of America; UK: United Kingdom; IQ: interquartile.

and studying pharmacy (57%). Among non-pharmacy participants, 40% were enrolled in other healthcare-related disciplines. Some students did not answer every question, and several questions were displayed only if a particular response was provided to a previous question, resulting in different numbers of responses for some questions. Table I provides additional details.

Vape Use

Just over half the participants (53%; n = 194/368) reported ever vaping in their life, though of the 194 vape ever-users, 71% (n = 138/194), had used them in the past but do not currently. In total, 15% (n = 56/368) of the complete survey sample reported they were currently vaping. Of the 56 who currently vaped, vaping frequency was reported as: less than once a month (2%); once a month (13%); once a week (29%); several times a week (21%); and daily (36%). In contrast 38% (n = 141/368) of all participants reported having ever used tobacco but only 11% were current users (n = 39/368). Among those that currently vaped, 13% (n = 7/56) reported using vapes for smoking cessation.

Vape use differed significantly for pharmacy and non-pharmacy students (p = 0.03); pharmacy students reported never (51%), occasional use in the past but no current use (32%), regular use in the past but no current

Tab. II. Motivations to vape or abstain from vaping.

Motivations regarding vaping or abstaining	Pharmacy n(%)	Non-pharmacy n(%)	P-value	UK n(%)	US n(%)	P-value
Motivations for vaping among those who vape currently						
Positive image	0/25(0)	3/31(10)	0.25	1/27(4)	2/29(7)	1.00
Peer pressure	3/25(12)	3/31(10)	1.00	2/27(7)	4/29(14)	0.67
Pleasurable feelings / "buzz"	19/25(76)	21/31(68)	0.50	19/27(70)	21/29(72)	0.87
Relaxation / stress relief	17/25(68)	14/31(45)	0.09	18/27(67)	13/29(45)	0.10
Nice taste	7/25(28)	14/31(45)	0.19	12/27(44)	9/29(31)	0.30
To help quit smoking	2/25(8)	5/31(16)	0.44	3/27(11)	4/29(14)	1.00
Perceived motivations why others vape among those who do not vape currently						
Positive image	104/182(57)	63/126(50)	0.22	103/186(55)	64/123(52)	0.56
Peer pressure	122/182(67)	83/126(66)	0.83	135/186(73)	70/123(57)	**0.01**
Pleasurable feelings / "buzz"	112/182(62)	75/126(60)	0.72	98/186(53)	89/123(72)	**<0.01**
Relaxation / stress relief	124/182(68)	67/126(53)	**0.01**	105/186(56)	86/123(70)	**0.02**
Nice taste	69/182(38)	53/126(42)	0.46	81/186(44)	40/123(33)	0.05
To help quit smoking	81/182(45)	59/126(47)	0.69	93/186(50)	47/123(38)	**0.04**
Motivations for abstaining from vaping among those who do not vape currently						
Negative image	57/182(31)	47/126(37)	0.28	62/186(33)	43/123(35)	0.77
Peer pressure not to vape	7/182(4)	5/126(4)	1.00	6/186(3)	6/123(5)	0.55
Bad smell or taste	45/182(25)	27/126(21)	0.50	45/186(24)	28/123(23)	0.77
Cost	79/182(43)	52/126(41)	0.71	86/186(46)	45/123(37)	0.11
Health consequences	169/182(93)	103/126(82)	**<0.01**	169/186(91)	105/123(85)	0.14
Risk of addiction	129/182(71)	70/126(56)	**0.01**	124/186(67)	76/123(62)	0.38
Not interested in vaping	127/182(70)	79/126(63)	0.19	122/186(66)	85/123(69)	0.52

Motivations and deterrents to use by area of study and university location; students who currently vape were asked about their personal motivations while students who did not vape were asked about what they perceived to be the motivations for others to vape and were also asked what motivated them to abstain from vaping. US: United States of America; UK: United Kingdom.

use (5%), current use occasionally (8%), and current use regularly (4%), while non-pharmacy students reported never (41%), occasional use in the past but no current use (28%), regular use in the past but no current use (11%), current use occasionally (12%) and current use regularly (8%).

Vape use between UK and US students surveyed did not differ significantly (p = 0.07); UK students reported never (48%), occasional use in the past but no current use (30%), regular use in the past but no current use (10%), current use occasionally (9%) and current use regularly (3%), while US students reported never (47%), occasional use in the past but no current use (30%), regular use in the past but no current use (4%), current use occasionally (10%) and current use regularly (9%).

Vaping frequency did not differ significantly based on degree or location.

Motivations for Use

The most commonly cited motivations for use among current vape users was pleasurable feelings (*e.g.,* "get a buzz") followed by relaxation/stress relief, and nice taste. Among non-vape users, the perceived motivations contained much more varied responses, with little difference in response rates among answer choices. Pharmacy students were significantly more likely to cite health consequences (93% *vs.* 82%; p < 0.01) and addiction risk (71% *vs.* 56%; p = 0.01) as deterrents than non-pharmacy students, respectively. There were no differences between UK and US students with regards to motivations for abstaining from vapes. See Table II for additional information.

Perceived Harms

Pharmacy and non-pharmacy students demonstrated significant differences regarding their perceived risk of vaping-related harm. Pharmacy students were more likely than non-pharmacy students to believe that: vapes contain cancer-causing chemicals (83% vs 73%, p = 0.05); exhaled vapor can negatively affect the health of other people (65% vs 53%, p = 0.02); and that vaping should be banned in public places (66% vs 55%, p < 0.01). Both groups expressed similar views regarding the relative risk of vapes versus traditional cigarettes, with the most common response in both groups being that vapes are 'slightly less harmful'. However, more pharmacy students believed that vapes are equally or more addictive than traditional cigarettes (88% vs 78% p < 0.01), and less pharmacy students believed that vaping is an effective method to help someone quit smoking traditional cigarettes (21% vs 35%, p = 0.01).

There were again, few significant differences between US and UK students with regards to perceived harms. However, significantly fewer US students believed

Tab. III. Perceived harms and addiction potential of vaping and perceived efficacy as a smoking cessation tool.

Item	Answer	Pharmacy n (%)	Non-pharmacy n (%)	P - value	UK n (%)	USA n (%)	P -value
Do vapes contain cancer-causing ingredients?	Yes	173/208(83)	115/157(73)	**0.05**	166/214(78)	123/152(81)	0.1
	No	6/208(3)	11/157(7)		7/214(3)	10/152(7)	
	Unsure	29/208(14)	31/157(20)		41/214(19)	19/152(13)	
Does exhaled vapor from a vape negatively affect the health of other people?	Yes	135/208(65)	83/157(53)	**0.02**	133/214(62)	85/152(56)	0.48
	No	21/208(10)	31/157(20)		29/214(14)	23/152(15)	
	Unsure	52/208(25)	43/157(27)		52/214(24)	44/152(29)	
Is vaping an effective method to help someone quit smoking traditional cigarettes?	Yes	44/205(21)	55/156(35)	**0.01**	70/210(33)	29/152(19)	**<0.01**
	No	101/205(49)	67/156(43)		75/210(36)	93/152(61)	
	Unsure	60/205(29)	34/156(22)		65/210(31)	30/152(20)	
Should vaping be banned in public places similarly to traditional cigarettes?	Yes	135/206(66)	86/156(55)	**<0.01**	144/211(68)	78/152(51)	**<0.01**
	No	26/206(13)	43/156(28)		31/211(15)	38/152(25)	
	Unsure	45/206(22)	27156(17)		36/211(17)	36/152(24)	
Do you believe vapes are more or less harmful than traditional cigarettes?	Much less harmful	11/208(5)	9/157(6)	0.70	12/214(6)	8/152(5)	0.49
	Slightly less harmful	97/20847(47)	66/157(42)		102/214(48)	63/152(41)	
	Equally harmful	67/208(32)	48/157(31)		67/214(31)	48/152(32)	
	Slightly more harmful	24/208(12)	24/157(15)		25/214(12)	22/152(14)	
	Much more harmful	9/208(4)	10/157(6)		8/214(4)	11/152(7)	
How easy do you think it would be to quit using vapes compared to traditional cigarettes?	Much less difficult	2/206(1)	12/157(8)	**<0.01**	5/213(2)	9/152(6)	0.17
	Slightly less difficult	44/206(21)	28/157(18)		49/213(23)	23/152(15)	
	Equally easy	78/206(38)	44/157(28)		73/213(34)	50/152(33)	
	Slightly more difficult	62/206(30)	48/157(31)		61/213(29)	50/152(33)	
	Much more difficult	20/206(10)	25/157(16)		25/213(12)	20/152(13)	
How addictive do you think vapes are compared to traditional cigarettes?	Much less addictive	2/207(1)	13/157(8)	**<0.01**	4/213(2)	11/152(7)	0.08
	Slightly less addictive	22/207(11)	21/157(13)		26/213(12)	17/152(11)	
	Equally addictive	106/207(51)	44/157(28)		84/213(39)	67/152(44)	
	Slightly more addictive	46/207(22)	41/157(26)		55/213(26)	31/152(20)	
	Much more addictive	31/207(15)	38/157(24)		44/213(21)	26/152(17)	

Perceptions regarding potential harms associated with vaping and their utility as a smoking cessation methodology by area of study and university location. US: United States of America; UK: United Kingdom

that vaping is an effective method to help someone quit smoking traditional cigarettes (19% *vs.* 33%, respectively, $p < 0.01$) and that vaping should be banned in public places (51% *vs.* 68%, respectively, $p < 0.01$) *vs.* UK students. Table III provides additional information.

Discussion

This study is among the first to compare vape use and perceptions among pharmacy and non-pharmacy students from two universities in different countries. As hypothesized, given pharmacy students' healthcare interest and training, vape use and perceived harms differed significantly between pharmacy and non-pharmacy students. Pharmacy students were less likely to vape and possessed a better understanding of their risks. However, few differences were observed based on which country the students studied in.

Given the important role pharmacists play in patient education, public health, and preventable medicine as the most accessible healthcare providers, and commonly the frontline for patient health questions, it is important that pharmacists are well aware of the potential risks of vaping and able to accurately educate patients on these risks. This will likely become even more important going forward, with vaping rates increasing, and as more states pass legislation granting pharmacists provider status or allowing pharmacists to independently provide prescription-only smoking cessation medications [14]. Thus, it was encouraging that pharmacy students were less likely to vape and significantly more likely to cite health consequences and addiction risk as deterrents to vaping than their non-pharmacy student counterparts. It's

possible this difference may have been more pronounced if not for the relatively high percentage of healthcare students in the non-pharmacy control group (40%), as these students may have also received education regarding vaping-related health concerns. Among the 31 non-pharmacy students who reported current vaping, 77% were in non-healthcare related courses and 23% were in other healthcare related courses. In the present study, pharmacy students also reported less use of traditional cigarettes or tobacco, cannabis, or alcohol as well, potentially indicating that their pharmacy interest or training confers them greater appreciation of the risks of substance use. However, despite the rates being lower than non-pharmacy students, it was still disconcerting that nearly half of all pharmacy students reported having vaped, with 12% reporting current vape use. Several recent papers have identified gaps in student pharmacists' knowledge regarding vaping versus traditional cigarettes and have called for increased education and a standardized vaping cessation curriculum across pharmacy schools [15-19]. Specifically, the pharmacy curriculum of both universities surveyed in the present study did include vaping related content prior to this study being conducted, though this may not be the case for all pharmacy schools. It is unclear if these results would be generalizable to schools that do not specifically address vaping within their curriculum.

There are limited studies regarding pharmacy student vaping to compare to the rates identified in the present study (49% ever use; 12% current use), and most are older studies that may not accurately reflect the present state. Two studies previously compared US pharmacy students to students from other health profession schools in the same university; a 2020 survey found pharmacy students were less likely to currently vape (6%) than other healthcare students (19%, $p < 0.001$) [13], while a 2014 survey found the rate of pharmacy students ever vaping (22%) was similar to the total sample of health profession students (23%) [12]. Outside of the US, a 2020 survey of male students from several Saudi Arabian health colleges found that 34.5% of pharmacy students had ever vaped, a numerically lower rate than medical (47.4%) and dental (40.7%) students, but not nursing students (32%) [20]. And among Serbian pharmacy students surveyed in 2016, only 9.9% reported ever vaping, though a much higher proportion (47%) reported ever smoking traditional cigarettes [21]. This rate of smoking traditional cigarettes was much higher than reported by pharmacy students in the present study (28%), likely indicative of cultural differences, as Serbia has one of the highest tobacco use rates worldwide [22]. Each of these previous studies identified lower pharmacy student vaping rates than the present study. Reasons for these differences are likely multifactorial, but may include increased vaping prevalence, vape acceptance, and vape accessibility over the past several years, cultural differences between the locations the studies took place, inclusion of only male students in one study, and different study designs and recruitment methods.

To the authors' knowledge, the present study was the first to simultaneously survey pharmacy students from multiple countries regarding vape use, identifying no difference between the US and UK students surveyed. The present study also identified similar responses regarding vaping-related risks between students from the two countries, seemingly indicating that vape use and perceptions may not greatly differ among the two student groups surveyed. While these two student groups should not be extrapolated to represent all students in the US or UK, the congruence observed in these two samples could be due to the greater cultural similarities between the US and UK *vs.* Serbia and Saudi Arabia, and the fact that these students were surveyed simultaneously using the same questionnaire.

However, in the present study, one interesting difference that did emerge between the students from the two universities, was that a significantly higher proportion of US students (61%) believed that vaping was not an effective method to help someone quit smoking traditional cigarettes compared to UK students (36%). This could be indicative of the UK's greater acceptance of vaping as a harm reduction method for those who use tobacco. Recently, the UK introduced the first national governmental program to distribute vaping kits as a tobacco cessation tool in an effort to reduce smoking rates in the country [23]. This was predicated on Public Health England's assertion that vaping is 95% less harmful than smoking traditional cigarettes, though some have questioned whether vaping truly produces that level of harm reduction [24-26]. Recent evidence does support vaping as a potentially efficacious tool to help people quit smoking, though it also indicates that many of these patients often continue vaping, potentially trading one harmful habit for another [27, 28]. Additionally, opponents worry that increased vape use, particularly in adolescents and young adults, may represent a gateway to future tobacco use [6]. Thus, whether or not vapes should be recommended as a smoking cessation tool remains unclear at this time, so it was not surprising that many students in the present study indicated they were unsure.

However, it is important that students realize that, while vapes may be less harmful than traditional cigarettes, they are not devoid of risks. A recent meta-analysis found that vaping significantly reduced respiratory disease risk but not cardiovascular disease risk and found that dual use (e.g., concurrently vaping and smoking traditional cigarettes) significantly increased patient harms [8]. The majority of students in the present study agreed that vapes were slightly less harmful than traditional cigarettes, and pharmacy students were less likely to support vaping as a smoking cessation tool than non-pharmacy students. Additionally, significantly more pharmacy students expressed concern regarding their carcinogenic effects and the negative impact of their vapor on others' health, as well as greater advocacy for public vaping bans. This ultimately suggests that, within this sample, pharmacy students had more negative attitudes towards vaping than non-pharmacy students. Sahr and colleagues similarly found pharmacy students to have a more negative

perception surrounding vapes than other health care students and that pharmacy students were less likely to agree that vapes are an effective method to help someone quit smoking traditional cigarettes than non-pharmacy students [13].

Limitations

The authors acknowledge several limitations of this study. First, survey respondents were recruited from two schools in the US and UK and may not be generalizable to all students in these countries or students of other universities or locations. Furthermore, the study was limited to current university students between the ages of 18-30 years, so results are not generalizable to individuals of similar ages who are not enrolled in a university or those from different age groups. Demographics collected were limited, and thus it is unclear how factors such as ethnicity or religion may have influenced trends in vape usage and perceptions. Other demographic factors that could have impacted the results but were not collected include the year of school the students were enrolled in and the specific program the non-pharmacy health care students were studying. Furthermore, given the many vape options on the market, additional information may be needed to identify nuances in vaping habits. For example, the survey did not identify what substances the students were vaping (*e.g.,* nicotine, flavored non-nicotine, or cannabis) which could affect the extent of harm and addiction risk students perceive. Lastly, because the investigators did not have a means of contacting all students outside of the pharmacy program, a different method was used to recruit non-pharmacy participants, which could have introduced selection bias into the control sample (*e.g.,* a fairly high proportion of the non-pharmacy students were studying other healthcare disciplines). However, despite these limitations, to the authors' knowledge, this study represents one of the largest studies comparing vaping rates of pharmacy versus non-pharmacy students and students studying at universities in different countries.

Conclusion

Vape use and harm perception significantly differed between the pharmacy and non-pharmacy university students surveyed, with pharmacy students less likely to vape and exhibiting heightened awareness of the associated risks than non-pharmacy students. However, few differences were observed between UK and US students in this sample.

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Conflicts of interest statement

The authors have no conflicts of interest to disclose.

Authors' contributions

SM: conceived and designed study; collected data; wrote first draft of manuscript. HO: performed analysis; revised manuscript. CF: performed analysis; revised manuscript. KE: conceived and designed study; collected data; wrote first draft of manuscript.

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HEALTH PROMOTION

The responsibilities of a commercial intermediation company as a new food business: the case of a typical regional Italian food

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Keywords

Food safety • Food business operator (FBO) • Food legislation

Summary

According to Regulation (EC) 178/2002, "any undertaking, whether for profit or not and whether public or private, carrying out any of the activities related to any stage of production, processing and distribution of food" must be classified as a "food business". A food business operator (FBO) is "the natural or legal person responsible for ensuring that the requirements of food law are met within the food business under their control". We analyzed the case of an Italian wholesale commercial intermediation company, purchasing a typically carbohydrate-rich local product from producers and reselling it to retailers, although never physically possessing it. In the marketing process, the company misleadingly emphasized the product's protein content, providing inaccurate nutritional information on the label, thus committing food fraud. Moreover, as required by European law, sanitary guarantees on the operating methods and traceability were not provided. To ensure food safety, every food business is subject to the obligation of registration (Regulation EC 852/2004), preparation of the self-control plan according to the principles of the HACCP system and traceability obligations (Regulation EC 178/2002). This case highlights the current general poor culture in food safety. It shows the urgent need for awareness-raising and training interventions to improve behaviors and clarify the qualifications and responsibilities of all parties involved, including FBOs and competent authorities, to prevent health risks and food fraud.

Introduction

The accountability of the food business operator (FBO) is a key point of the current European food legislation. Indeed, they bear the primary responsibility for ensuring food safety.

In particular, Regulation (EC) No 178/2002 ("General Food Law") [1], identifies the FBO as the natural or legal person responsible for ensuring compliance with the provisions of the legislation in the food business under their control. This approach is grounded in Recital 30 of the same Regulation, which states that: "A food business operator is best placed to devise a safe system for supplying food and ensuring that the food it supplies is safe; thus, it should have primary legal responsibility for ensuring food safety". The same Regulation introduces the fundamental principle of an integrated supply chain approach, encompassing all stages of production, processing and distribution; specifically, for the final stage of the supply chain, it defines placing on the market as "the holding of food or feed for sale, including offering for sale or any other form of transfer, whether free of charge or not, and the sale, distribution, and other forms of transfer themselves".

The EU regulatory framework evolved until the entry into force of the "Hygiene Package" in 2006, which definitively consolidated and standardised the general principles of food safety legislation at the European level. In this context, Regulation (EC) 852/2004 [2] reaffirms that FBOs must ensure hygiene requirements at all stages of food production, processing and distribution by applying self-control, according to the principles of the HACCP (Hazard Analysis Critical Control Points) system. Self-control derives from the above-mentioned empowerment of the FBO and corresponds to the obligation to keep its production under control.

Among the FBO's obligations is also the guarantee of product traceability, defined in Regulation (EC) No 178/2002 [1] as "the ability to trace and follow a food, feed, food-producing animal or substance intended to be, or expected to be incorporated into a food or feed, through all stages of production, processing and distribution;". The 'Hygiene Package' then extended this obligation to all agri-food products, making it possible to identify any product at any stage of the production cycle.

Lastly, Article 6 of Regulation (EC) 852/2004 [2] regulates the obligation of registration, stipulating that FBOs must notify the Competent Authority for Food Safetyof every food business under their control carrying out any food production, processing, transport, distribution, sale and administration activity, and any

significant change in activity so that the Competent Authority has up-to-date information at its disposal at all times.
The identification and qualification of the FBO, however, are relevant critical issues in light of the increasing complexity and extension of the agri-food supply chain, including the sales phase, the fragmentation of processes, the variety and number of actors involved, and the complexity of both ownership and logistical steps [3]. In particular, the rapid expansion of e-commerce in the food sector has brought to light the complexities and gaps inherent in the definition culture of the roles and responsibilities of operators involved in online food trading, including Internet service providers [4]. Among the obligations falling on the FBO, the most neglected has been identified as the one relating to the traceability of food products. A study published by Mettevi M et al. [3] identified among the main barriers to fulfilling the obligation of traceability the increasing complexity of food chains and the lack of specific personnel training.
This non-compliance has also been linked to the growing risk of food fraud offences, the prosecution of which, however, is made particularly complex by the large number of actors involved in the chain, many of whom frequently do not physically possess the foodstuff. In this context, Manning highlighted in a study published in 2016 [5] that, in order to mitigate the issue of food fraud, it would be advisable to implement an ongoing development of data centralisation systems, in particularly ensuring that separate databases can be coordinated to add value through collective data analysis, and secondly, ensuring that there are appropriate deterrent mechanisms in place so that food fraud mitigation moves from a fraud detection to a fraud prevention stance [6].
Roth et al. [7] identified globalization as a factor associated with the difficulties in fulfilling the obligation of traceability of food products and the risk of committing food fraud. The global relevance of these issues and the need to develop new approaches that can be used by Control Authorities to verify and ensure the safety and traceability of food, as well as to protect producers and industry from unfair competition, are evident. Such actions can only increase consumers' trust in the purchased food [8].
In order to illustrate the aforementioned increasing complexities related to the articulations of the food chain and the qualification of FBOs, a case study will be described, handled through the collaboration of various Authorities and control bodies for compliance with food legislation [9], such as the Food Hygiene and Nutrition Services of the Local Health Authorities operating in the Northwest area of Italy, under the coordination of the Italian Ministry of Health. The case concerns a food brokerage company failing to comply with the main obligations falling on the FBO as provided by EU food legislation. Specifically, those related to registration, self-control procedures, and traceability of food products. Additionally, this company marketed under its own brand typical regional bakery products, whose traditional recipe involves a predominant carbohydrate component, with nutritional values on the label reformulated in favour of the protein component, which was found to be false during the investigations.

Materials and methods

The investigation focused on the food chain structure and the specific roles of the involved FBOs (Tab. I). The processes that supported the findings of non-compliance to food safety European legislation and the consequent administrative contestation applying Italian laws by Competent Authorities will be highlighted. Finally, criticisms in current identification of new types of FBOs and education about FBOs obligations described by food safety European legislation will be discussed.

Results

In 2021, investigations concerning the falsification of nutritional values reported on laboratory analysis of typical regional bakery products marketed under the same brand name in different types were initiated by the Italian Judicial Authority.
As a result, the owner of the food company whose brand appeared on the labels of the bakery products under investigation was identified as responsible, resulting in charges of commercial fraud.
Regarding the production and distribution chain of these products, it was also ascertained that the aforementioned company, after an initial phase of direct production in a laboratory managed by the company owner, which later became an intermediary only, would then delegate production to another company primarily engaged in bakery activities. However, it provided recipes, raw materials, boxes, and other packaging materials, including rolls of original labels to be affixed to the packaging of the finished product. The bakery was responsible for all product processing, from dough formation to baking and packaging of the finished product, including batch production. During the investigations, the bakery stated that it conducted no internal quality checks, neither on the raw materials received from the intermediary's suppliers nor on the finished product, following an agreement between the parties that delegated this responsibility to the ordering company, identified as the intermediary. Additionally, no formal contract had been concluded between the intermediary and the bakery.
Initially, product storage was entrusted to a logistics company or an agricultural cooperative's warehouse.
The logistics company directly handled the distribution to retailers nationwide, while the warehouse manager entrusted the packages to a courier for delivery to the end customers. Subsequently, investigations revealed that the sole director of the intermediary company with intermediary activities had changed the shipping and delivery methods of bakery products to customers, managing the collection directly with the courier, who in

Tab. I. Time scan of case study events: main activities conducted by the Official Control Authorities.

Date	Event
June 2021	Search at the residence of the legal representative of the company with intermediary activity, seizure of false laboratory analysis reports, inspection at the bakery, checks on the registered office of the company with intermediary activities, and on the activity cessation of one local unit from October-November 2018.
21 December 2021	Partial conclusion of investigations on the production and marketing among the Italian territory of typical regional bakery products with the same brand bearing false nutritional values on the label.
08 August 2022 and 06 September 2022	Further inspection at the bakery: verification of production methods and product supply agreed with the company with intermediary activities.
15 September 2022	Identification of irregularities on the address of the registered office and on the local unit with productive activity subject to notification.
29 September 2022	Inspection at the logistics company: assessment of new methods of shipping products prepared by the sole administrator of the food company acting as an intermediary.
11 November 2022	Information collection report (under the Art. 13 L. 689/1981 and Art. 137 Reg. (EU) 625/2017) in the presence of the legal representative of the company with intermediary activity.
15 November 2022	Information collection report (under the Art. 13 L. 689/1981 and Art. 137 Reg. (EU) 625/2017) at the associated firm of accountants indicated as the registered office in the Company's Chamber of Commerce record with intermediary activity in the presence of the legal representative of the company with intermediary activities.
23 November 2022	Notification of complaints of administrative violations and setting of the deadline (Art. 6 c. 7 Legislative Decree 193/2007 and Art. 138 Reg. (EU) 625/2017) to the legal representative of the company with intermediary activity.

turn delivered directly to the recipient indicated by the intermediary each time. The intermediary coordinated the activities of the various companies involved.

Among how the products were sold, it was ascertained that the company with intermediary activities had a website and Instagram page, but also that the products were sold on numerous other sites dedicated to the sale of 'healthy, dietetic, protein' and 'sports nutrition' products.

With regard to the checks carried out on the registration of establishments and traceability of food products, as required for all food businesses by Article 6 of Regulation (EC) 852/2004 [2] and Article 18 of Regulation (EC) 178/2002 [1], it had emerged that the registered office of the intermediary, a crucial address in cases of a potentially unstructured intermediary commercial activity, corresponded to the address of a corporate and tax consultancy firm.

The latter reported that he had not been assisting the intermediary for some time, contrary to what the intermediary's owner asserted (stating that he deposited accounting records with invoices and transport documents (DDTs) at this firm). In order to alternatively obtain such documentation useful for verifying the traceability the products, further investigations were carried out at the producing bakery. The first DDTs examined, with the bakery's name as the sender addressed to the intermediary and destined to the courier, did not indicate the quantities of the products or their final destination, indicating that the intermediary formally purchased the commissioned products from the bakery and defects in the traceability path of the products.

It also emerged that the only local unit with production activity where an industrial oven had been installed and registered as required by Regulation (EC) 852/2004 [2] had been inactive since the end of 2018, although the cessation had not been notified to the competent Local Health Authority (ASL) as required by the aforementioned Regulation.

At the time of the inspections, moreover, the establishment was still listed in the Chamber of Commerce records, an official information document that includes personal, legal, and tax information of Italian companies registered in the business registry, specifying production and trade activities of bakery products.

These findings highlighted the food business's failure to fulfil the obligations of registration and traceability of food products required by European legislation.

Regarding the contestation about food fraud, the intermediary argued that the products had changed in denomination, composition, and labelling. It also reported that it had not received any reports regarding human health safety profiles from consumers. However, the Official Control Authorities responsible for the investigations noted that the intermediary had not provided them with documentation regarding the new formulation of the products nor demonstrated compliance with the falling obligations on the FBO according to European legislation on food safety.

Further investigations conducted by the Food and Nutrition Hygiene Service of the A.S.L. in accordance with European legislation on official controls [9] had allowed the collection of information directly from the intermediary company's manager, regarding:

- the predominant characteristics and the type of consumer to whom the own-brand products were intended, respectively "protein and gluten-free characteristics" and "people who engage in sports or have intolerance problems";
- the individual responsibility in formulating the recipes, represented by consultants identified by the intermediary itself; the process of selecting ingredients based on the characteristics outlined in

the technical sheets and other documentation; the implementation of internal checks at accredited laboratories to assess the nutritional values of the products;
- the operating methods of the bakery, which received the recipes and production procedures for the individual types of products from the intermediary and carried out production and packaging;
- a further establishment used as a food distribution platform, which was the subject of a recent notification (which had not been received by the competent territorial authority at the time the information was collected) and for which the self-control plan based on HACCP principles was being prepared;
- the documentation related to product traceability and labelling, particularly nutritional labelling, which the intermediary claimed to be held at their residence rather than at the registered office specified in the Chamber of Commerce extract of the company; it was also reported that transportation documents and invoices were issued directly and that the predominant clientele consisted of other businesses rather than individual consumers, such as gyms, shops, and pharmacies;
- the product traceability procedure, represented by a database prepared and updated daily by the intermediary, shows the invoice number of the finished products that the intermediary purchased from the bakery and the relevant lot and expiry date numbers associated with the invoice numbers of the sales by the intermediary to the final customers; concerning the traceability of the raw materials sold by the intermediary to the bakery, the manager reported that he reported the lot number on the sales invoices;

Furthermore, the intermediary company's manager had put forward several reasons for:
- the lack of registration of the commercial intermediary activity, represented by the fact of "not directly producing anything";
- the failure to draw up a self-control plan based on the principles of HACCP for the commercial intermediary activity, consisting in the fact that he did not see or produce the products directly but only provided the bakery with the recipes and labels to be affixed to them; the bakery was directly responsible for identifying deadlines and was also mentioned on the labels as the producer;
- the failure to communicate the cessation of production activities was due to their unaware of this obligation under Article 6 of Regulation (EC) 852/2004 [2].

Following the investigations carried out, the Food and Nutrition Hygiene Service proceeded with the administrative contestation, as provided for by the Italian sanctioning system [10], and set deadlines [9] aimed at resolving the non-compliances contested by the manager of the commercial intermediary company, violations of Articles 5-6 of Regulation (EC) 852/2004 [2] and Article 18 of Regulation (EC) 178/2002 [1] for the reasons described below:

- the failure of the FBO to fulfill the obligation of registration and notification of significant changes in activities related to the food chain as provided for in Article 6 of Regulation (EC) 852/2004 [2], preventing local competent authorities from having updated information regarding the company and offering them poor collaboration: indeed, the cessation of activity of the local production unit, the change in the conduct of the food business activity through the sale of raw materials to the producing bakery and the purchase of finished products from it, and the performance of an activity attributable to commercial intermediation had not been notified; furthermore, even the Chamber of Commerce extract was not updated in terms of registered office, email contact, production units, and related activities; the intermediary's personal computer kept at home had been identified by the intermediary as the "place" for storing documentation related to product traceability, but the home address had never been formally communicated to the competent authorities as a facility connected to the company's activities;
- the lack of procedures based on the principles of the HACCP system for food distribution activities, in the application of Article 5 of Regulation (EC) 852/2004 [2], the commercial intermediary company of food products must be classified as a food business, even though it does not directly produce food, simply because it distributes them, moreover with its brand and identifying mark. As a food business, the intermediary must, therefore, have its self-control plan, including procedures and systems to ensure the traceability of the food handled;
- the absence of an effective traceability system provided for in Article 18 of Regulation (EC) 178/2002 [1]: the examination of a sample from one of the databases held by the intermediary, some invoices, and the related product labels examined, had highlighted the failure to update the product name and the lack of correspondence between the products actually sold recorded in the database and the description of the products listed in the purchase invoices from the bakery and sales invoices to customers; the database indicated invoice numbers but not product quantities, the latter being specified only in the invoices; the invoices, however, lacked batch numbers and expiration dates; the labels of the products with a new name indicated a minimum term of conservation and not an expiration date, unlike the previous formulations, but the database still mentioned the expiration date (no longer applicable to the newly formulated products) among the data required by the traceability system; finally, a discrepancy was noted in the data entry criteria used to record incoming products in the database compared to those for outgoing products, as the specification of the company name to which the products were sold was not provided.

The manager of the commercial intermediary activity filed an appeal against the aforementioned contestations,

reaffirming that they only engage in the sale of raw materials and finished products without intervening in the production, packaging, and transportation phases, and therefore believing that they are not subject to the obligations of OSA as provided for by European food legislation. They denied the need to communicate the cessation of production activity at the local unit registered under Article 6 of Regulation (EC) 852/2004 [2], adding that such omission does not cause any harm or potential danger to consumers, nor does it prejudice any official controls [9], considering that production does not take place in an "unknown" or "non-updated" facility. They also stated that they had prepared a self-control plan based on HACCP principles, although they believed that this requirement was only necessary for operators managing the production and delivery of food products; in this context, they emphasized the professionalism of the consultants selected for recipe formulation and raw material selection, as well as the internal checks carried out regarding the quality standards of the production, logistics, and transportation companies. Finally, they attributed the contested issues regarding the traceability system to material errors and reported that they had taken steps to resolve them. However, the competent ministerial authority formally supported the aforementioned appeals.

Discussion

The case described provides insights into the growing challenges related to the awareness of the qualifications of the FBO and their obligations and, consequently, the competent authorities' correct qualifications of such figures.

In particular, when the FBO's activity does not explicitly involve direct handling of food products, its awareness of having to qualify as such may not be immediate. This includes the increasingly complex management of distribution and indirect sales phases (online trade, mere logistics activity and trade in pre-packed non-perishable products). However, even in these cases, the operator qualifies as a FBO and is bound by all the obligations that food legislation imposes, including registration through notification, the preparation of a self-control plan consistent with its activities, product traceability and, in the event of suspected/confirmed non-conformity of the product distributed, cooperation in product recall or withdrawal procedures, and collaboration with authorities and other operators involved.

The Italian Ministry of Health has managed this issue through a formal Communication addressed to all control authorities already in 2012 [11], referring also to the “Guidance document on the implementation of certain provisions of Regulation (EC) 852/2004 on the hygiene of foodstuffs” issued by the European Commission on 16/02/2019 [12]. This communication clarified that "even the company operating in the field of commercial intermediation, which deals with the movement of food products between suppliers and between these and retailers – without necessarily involving the handling of food products or their storage at the company's premises, which may consist only of an office – is subject to the registration obligation. "It reiterates that "the intermediation activity therefore fully falls within the definition of a food business operator whenever it is connected to one of the stages of food production, processing, and distribution".

The Communication also evaluates the definition of "supplier" offered by Regulation (EC) 178/2002 [1] as generic, as it can refer indiscriminately to both the owner and the holder of the goods, since products, once they leave the production facility, can undergo different ownership and logistical stages. Therefore, the owner of the holder of the goods may not coincide with the physical holder of the same. It clarifies that "food business’ means any undertaking, whether for profit or not and whether public or private, carrying out any of the activities related to any stage of production, processing and distribution of food". Regarding the registration obligations, it further explains that "the unit to be registered is represented by the offices where commercial documents are kept" and that "the owner of the business is required to submit the SCIA (Certified Notification of Start of Business) in the municipality where these offices are located, declaring that it is an intermediary activity". It concludes that such an FBO is not subject to the general and specific hygiene requirements provided by current regulations but to the traceability, withdrawal, and recall obligations under Regulation (EC) 178/2002 [1].

It is noted that the European legislator, about the notification obligation, refers to "every establishment" under the control of the FBO [2] and not generically to the food business defined in Reg. (EC) 178/2002 [1] as “any public or private entity, with or without profit, which carries out any of the activities connected to one of the phases of food production, processing, and distribution." This clarification may imply an intention to make the competent authorities aware of detailed data regarding the composition of the food business. However, it may also introduce interpretative challenges, especially for FBOs that do not have physical premises where they carry out their activities, as can happen in the cases described above. An explicit clarification in this regard is provided by the recent amendment of Regulation (EC) 853/2004 [13], which introduced the definition of “intermediary operator” as “a food business operator, including traders, other than the first supplier, with or without premises, who carries out its activities between production areas, relaying areas or any establishments.” However, the definition was introduced with specific reference to the live bivalve mollusc chain [13]. Therefore, there is speculation about the opportunity to introduce specific regulatory enhancements (at least at the European level) regarding the e-commerce sector of food products, which is rapidly expanding, to enhance transparency and reliability. This could be achieved, for example, by clearly defining the roles and responsibilities of different operators, including Internet service providers, in the online food trade sector [4].

This is also aimed at reducing the risk of fraudulent activities occurring. Among the priority obligations of the FBO identified by the European legislator is also that of guaranteeing the traceability of foodstuffs by means of declaring to the competent authorities, upon request, the data relating to the suppliers of the products and the persons to whom the goods have been delivered. This is done in order to reconstruct every stage of the food's journey through the supply chain. However, even concerning this obligation, there is evidence of a lack of awareness and training for stakeholders [14, 15].

Self-monitoring in the phases following primary production must include the application of both Good Manufacturing Practices (GMP) and procedures based on the principles of the HACCP system. This system aims to identify, control, and mitigate food safety hazards using a concrete analysis of each process stage. FBOs must retain and provide, upon request, to the competent authorities' documentation proving the effective application and updating of procedures suitable for their purposes and consistent with operational reality. Even an FBO acting solely as an intermediary in food trade is obligated, as argued above, to establish, implement, and maintain one or more permanent procedures based on the principles of the HACCP system. Moreover, the same FBO must justify (with a documented qualification procedure) the choice of suppliers and storage and transportation companies and indicate based on what agreements (physical, chemical and microbiological specifications) the products subjected to commercial intermediation are purchased.

Consumer information profiles also emerged from the case. In this context, the European legislator has established that all foodstuffs placed on the market must bear the mandatory information on the label, including the possible presence of allergens, the conditions of use and storage, and the expiry date; in particular, the European legislation [16] emphasises the primary responsibility of the owner or manager of the brand under which the product is marketed, but also refers to the concurrent responsibility of the distributor who sells or offers for sale products whose non-compliance with the regulations in force may be presumed.

Lastly, it is important to have a network organisation between competent authorities, clearly distinguishing roles and responsibilities. In Italy, the current Legislative Decree 27/2021 art. 2 designates the Ministry of Health [17], the Regions, the Autonomous Provinces of Trento and Bolzano, and the Local Health Authorities, within their respective competencies as competent Authorities to carry out official controls in food businesses and to ascertain and contest administrative sanctions for violations concerning food, feed, animal health and welfare, animal by-products, plant protection products and pesticides. The same article provides that 'the Ministry of Health, in its capacity as Competent Authority, may avail itself of the NAS (Antisofistication and health nucleus of Carabinieri, guaranteeing the coordination of assessment activities with the control activities carried out by the other territorially competent authorities'.

In conclusion, for Article 2 of Regulation (EC) 178/2002 [1], "any undertaking, whether for profit or not and whether public or private, carrying out any of the activities related to any stage of production, processing and distribution of food", including a wholesale intermediary company that purchases food from producers and resells it to retailers, even without physically possessing the products, must still be qualified as a "food business" solely for the fact of carrying out a food distribution activity. Especially if, as in the case at hand, the brand displayed on the finished products belongs to the intermediary company. According to mandatory regulations, such a company is subject to the obligations of:

- registration (health notification) under Article 6 of Regulation (EC) 852/2004 [2];
- establishment of a self-monitoring plan according to the principles of the HACCP system referred to in Article 5 of Regulation (EC) 852/2004 [2];
- traceability and recall obligations under Articles 18 and 19 of Regulation (EC) 178/2002 [1].

A significant gap in food safety culture persists even two decades after the adoption of EU food regulations. The very recent Regulation (EU) 2021/382 [18] addresses this point by introducing a new chapter aimed explicitly at raising stakeholders' awareness on the issue to increase awareness and improve the behaviours of all involved parties, including competent authorities. Implementing training interventions for OSAs and their staff can be a useful strategy to enhance awareness and the significance of associated responsibilities.

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INFECTIOUS DISEASES

Giovanni Battista Grassi (1854-1925): a forgotten Italian scholar and his fundamental studies on malaria

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Keywords

Giovanni Battista Grassi; history of malaria; infectious diseases; tropical diseases, Charles Louis Alphonse Laveran

Summary

A century ago, on May 4, 1925, an Italian doctor, zoologist, botanist, and entomologist Giovanni Battista Grassi (1854-1925) died in Rome. He was known for his studies on malaria, and he was one of the founders of the "Italian school of malariology". At that time malaria was a main problem in the colonies for the military and in the tropics is a common disease that causes high fever and other symptoms. When the French chemist Louis Pasteur published his germ theory in the 1860s, scientists began to consider that an organism, might be responsible for the malaria disease and the breakthrough came in 1880 with Alphonse Laveran (1845-1922). It was therefore clear that many diseases are caused by microorganisms, and several scholars began to assume that also malaria was caused by a bacterium. Laveran recognized the parasite group that caused the infection in human beings; however, his studies were challenged. In 1889 Laveran showed that malaria is caused by another type of single-celled organism, a protozoan of the Plasmodium family, which attacks red blood cells and also identified other single-celled parasites that cause other diseases: there are four main types of malarial infection caused by four species of parasite plasmodium. In 1898 Grassi began a study that represented a turning point in the study and treatment of the disease. The authors aim to retrace the main steps in the historical evolution of this dangerous, infectious disease and they believe it's important to evoke the scientific personality of the Italian scientist Grassi who is one of the protagonists in the history of medicine and zoology between the 19th and 20th centuries, mainly because of his famous research, about the identification of the vector of human malaria.

Background

Exactly 100 years ago, on May 4, 1925, Giovanni Battista Grassi (1854-1925) (Fig. 1), an Italian doctor, zoologist, botanist and entomologist, known for his studies on malaria, died in Rome.

Grassi was among the scholars who founded the Italian school of malariology, which, after the discovery by the French doctor and army officer working in Algeria Charles Louis Alphonse Laveran (1845-1922) [1, 2] of the protozoan responsible for the infection in the red blood cells of malaria patients, played an important role in the study and prevention of this disease [3].

In 1907, Laveran (Fig. 2) was awarded the Nobel Prize for Medicine for his discovery [4, 5] and established the Laboratory of Tropical Diseases at the Pasteur Institute. In the year following (1908) he also founded the *Société de Pathologie Exotique*.

Between the end of the 19th century and the mid-20th century, malaria was endemic in Italy [6]. In the northern regions of the country, except for the coastal areas of Veneto, a mild form of the disease prevailed, while an extremely severe form raged in the southern regions and on the islands. In the Kingdom of Italy, the first public health statistics, which were published in 1887, revealed that malaria was endemic in approximately one third of the country, causing 21,033 deaths – a mortality rate of 710 cases per million inhabitants [7]. In the following decade, malaria killed 15,000 people per year [8]

Fig. 1. Giovanni Battista Grassi (Public Domain - Wikipedia commons).

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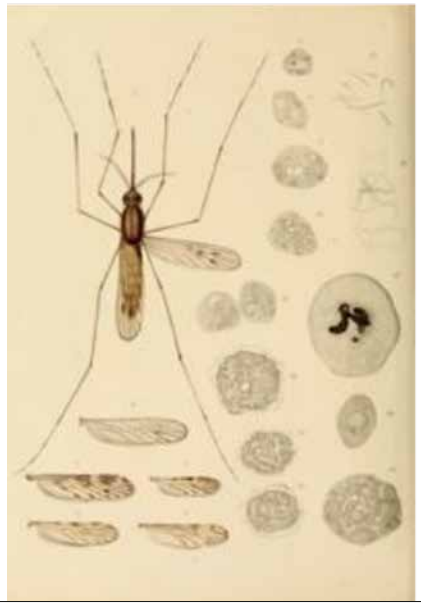
Fig. 2. Charles Louis Alphonse Laveran (Public Domain. Wikipedia commons).

Fig. 3. Original drawing by G.B. Grassi illustrating the cycle of malaria transmitted by the *Anopheles* mosquito (G.B. Grassi, *Studi di uno zoologo sulla malaria*).



and constituted one of the most serious public health problems in Italy at the time [9]. This was the context in which G.B. Grassi worked.

After graduating in Medicine in Pavia, Grassi became a professor of zoology, anatomy, and comparative physiology at the University of Catania in 1883, where he began to study malaria in birds. In 1890 he published the monograph "*Ueber die Parasiten der Malaria"* (On Malaria Parasites) in the journal "Zentralblatte für Bakteriologie und Parasitenkunde" (Central Journal of Bacteriology and Parasite Science), in which he described the malarial cycle in various species of birds, such as the owl, the pigeon and the sparrow [10].

In 1895, Grassi was appointed Professor of Comparative Anatomy at La Sapienza University in Rome. "In Rome, Grassi came into contact with the group of Roman malariologists, who convinced him of the validity of the transmission of *Plasmodium* via a hematophagous insect, a hypothesis he had until then considered doubtful. The problem was to identify the incriminated insect with certainty" [11, 12].

Subsequently, on studying the case of a patient at the Roman hospital of Santo Spirito in Sassia, together with Amico Bignami and Giuseppe Bastianelli, Grassi managed to demonstrate in 1898 that malaria was transmitted by mosquito bites. On 22 December 1898, he sent a communication to the Accademia dei Lincei in which he described the entire development cycle of *Plasmodium* in the body of *Anopheles claviger* [13]. Thus, the enigma of malaria transmission was solved.

Between 1898 and 1899, by mapping all the mosquito species present in the malarial and non-malarial areas of Italy, Grassi was able to correlate the presence of malaria with a specific genus of mosquito: only *Anopheles* could act as a vector of the human malarial parasite [14]. In this way, Grassi paved the way in the fight against malaria. In his volume *Studi di uno zoologo sulla malaria (A Zoologist's Studies on Malaria)* [15], which was published in 1900 by the *Reale Accademia dei Lincei*, Grassi summarized all the procedures and conclusions of his years of study on the *Anopheles* mosquito and on *Plasmodium* (Fig. 3).

However, his glory was overshadowed and, according to some, usurped by another scholar, the English doctor Ronald Ross (1857-1932). A few years earlier, in 1894, Patrick Manson (1844-1922), who is regarded as the father of tropical medicine, and to whom Grassi had dedicated his volume "*A Zoologist's studies on Malaria*", had hypothesized that mosquitoes played a fundamental role in the transmission of malaria [16].

He had therefore asked his colleague Ronald Ross to examine this thesis. Thus, in 1897-98, while in India, Ross found that an avian *Plasmodium* was transmitted by mosquitoes and hypothesized that human malaria also had a similar cycle.

In the first issue of the *Annales de l'Institut Pasteur* in 1899, Ross published an article entitled *"Calcutta, 31st December 1898: Du rôle des moustiques dans le paludisme (the role of mosquitoes in malaria"* [17].

The vector responsible for the transmission of the disease was indicated as a "moustique d'une nouvelle espèce" ("mosquito of a new species"): a "gray" or "spotted-winged" mosquito, names that are absolutely invalid in terms of Linnaean nomenclature. Not being a zoologist, Ross was obviously unfamiliar with zoological systematics, which Grassi knew very well.

Ross, however, was unable to demonstrate that malaria was transmitted to humans by mosquito bites, nor to establish that only one genus of mosquito, *Anopheles*, could act as a vector of the human malarial parasite, phenomena

which were ascertained by Amico Bignami, Giuseppe Bastianelli and Giovanni Battista Grassi. Indeed, in both humans and mosquitoes, these three Italian researchers described the developmental cycle of the three species of malarial parasites present in Italy [14].

The issue gave rise to a heated controversy between Grassi and Ross, who was awarded the Nobel Prize for Medicine in 1902 "for his work on malaria, by which he has shown how it enters the organism, and thereby has laid the foundation for successful research on this disease and methods of combating it" [18].

It has even been suggested that an English doctor, Thomas Edmonston Charles (1834-1906), who had visited the laboratories of Grassi and the other malariologists at the *Santo Spirito Hospital* in the period 1897-1898, may have reported to Ross the information that he had gathered there. When the dispute arose as to who had first discovered the vector responsible for the transmission of malaria, Ross made public the letters he had received from his colleague Charles [19].

At the end of 1900, Ross launched a defamatory campaign against the three Italian biologists, claiming that he was the first to discover the mechanism of transmission of malaria, in an attempt to bolster his chance of winning the Nobel Prize. Grassi reacted harshly to the accusations, which, in his opinion, cast doubt on his honor as a scientist. The true nature of the dispute, however, lay in the different ways of approaching research; Grassi's method was characteristic of zoological research – systematic, comparative and experimental – while the approach adopted by Ross was empirical and intuitive. Most probably, we can assert that Ross was the first to conclude that mosquitoes transmitted malaria, while Giovanni Battista Grassi was the first to identify *Anopheles* as the vector of the disease.

Considering this dispute, the Royal Swedish Academy of Sciences wanted to share the prize, but decided to seek arbitration and appointed the great German scientist Robert Koch (1843-1910) as the arbitrator. Unfortunately for Grassi, however, Koch did not prove to be unbiased. Indeed, he did not look favorably upon the Italian scholar, with whom he had argued in the spring of 1898, when he was in Maremma (Tuscany, Italy) to conduct his own studies on malaria.

On that occasion, Grassi had expressed his disagreement with the analytical methods of the German microbiologist. And so it was that the Nobel Prize was awarded only to Ronald Ross, who did not even mention Grassi and his studies in his acceptance speech.

This decision by the Royal Swedish Academy of Sciences was not accepted by Grassi, who decided to abandon his studies on malaria and devote himself to other research topics, only returning to the study of malaria at the end of the First World War, when the disease displayed a severe resurgence. Indeed, owing to the direct and indirect consequences of the war, deaths from malaria rose from 57 per million inhabitants in 1914 to 105 in 1915, to 237 in 1917 and to 325 in 1918 [20].

-Faced with this situation, Grassi resumed his research and in 1918 founded a "Malaria Observatory" in Fiumicino, in the river Tiber delta, where he carried out research on the flying habits of mosquitoes and on the incidence of malaria in the area. He suggested methods of disease control, initiating anti-malaria prophylaxis and saving the lives of hundreds of farmers and workers [21]. He also studied the populations of *Anopheles* in the Naples area, in the Province of Lucca and near Pavia, where the presence of *Anopheles claviger* was not accompanied by malaria. This research enabled him to ascertain the existence of a species of *Anopheles* that does not bite humans but only animals.

Grassi died in 1925, just as Paris Green was beginning to be used against malaria in Italy and Achille Sclavo [22], President of the Italian Association for Hygiene, returned to the subject of malaria in Sardinia by inaugurating the third National Congress on Hygiene [23]. In fact, in 1910, with the pathologist Alessandro Lustig (1856-1937), Sclavo had been the head of the first anti-malaria campaign in Sardinia, promoted by the Government as part of National Healthcare Policies for the prevention of infectious diseases. The campaign supported the reorganization of healthcare with doctors assigned to therapy and prophylaxis by means of State Quinine, but also gave rise to environmental remediation works and hygiene education [24, 25].

Also in 1925, the Italian Association for Hygiene printed its "*People's Instructions against Malaria*", which recommended specific rules of hygiene [26] in order to prevent the disease and the use of quinine [27], to be administered also through "painless injections", as stated in the advertisements for "Gelochin", which was produced by the Tuscan Serotherapy Institute (Fig. 4).

In these few pages of instructions, we can discern the thought of the great hygienist Sclavo, whose note to the text read: "It is strongly recommended that the Municipalities where malaria is present should distribute these instructions widely, especially among Elementary School children, and charge teachers to explain them and to demonstrate, also through visits and experiments, the appropriate means of fighting malaria" [28, 29].

Sclavo was a great believer in so-called "bottom-up education", whereby the young would carry the message of good practices to their elders, parents and relatives, who would then recognize the importance and usefulness of such practices.

In the hundred years that have passed since Grassi's death, Italy and many other countries have been declared free from malaria [30].

From 1944 onwards, the results yielded by the use of DDT (dichlorodiphenyltrichloroethane) were fundamental. When sprayed into the environment, DDT proved effective in reducing the mosquito population and the level of disease transmission [31].

Considerations on the current situation of malaria in the world

Nevertheless, malaria continues to claim lives, though encouraging data are being recorded in many areas [32].

Fig. 4. Advertisement for Gelochin, produced by the Tuscan Serotherapy Institute (Archive of the Gruppo Amici Sclavo).

Indeed, in the 25 years since 2000, approximately 2.2 billion cases of malaria and 12.7 million deaths have been avoided as a result of health policies [33]. In the same period, 44 countries and one territory have been certified as malaria-free [34].

Most recently, in October 2024, Egypt was officially declared malaria-free by the World Health Organization (WHO) (Fig. 5).

However, malaria remains a serious threat to public health, as is demonstrated by the highly significant figures released by the World Health Organization in its *2024 World Malaria Report* [35]. Indeed, 263 million cases of malaria were estimated in 2023.

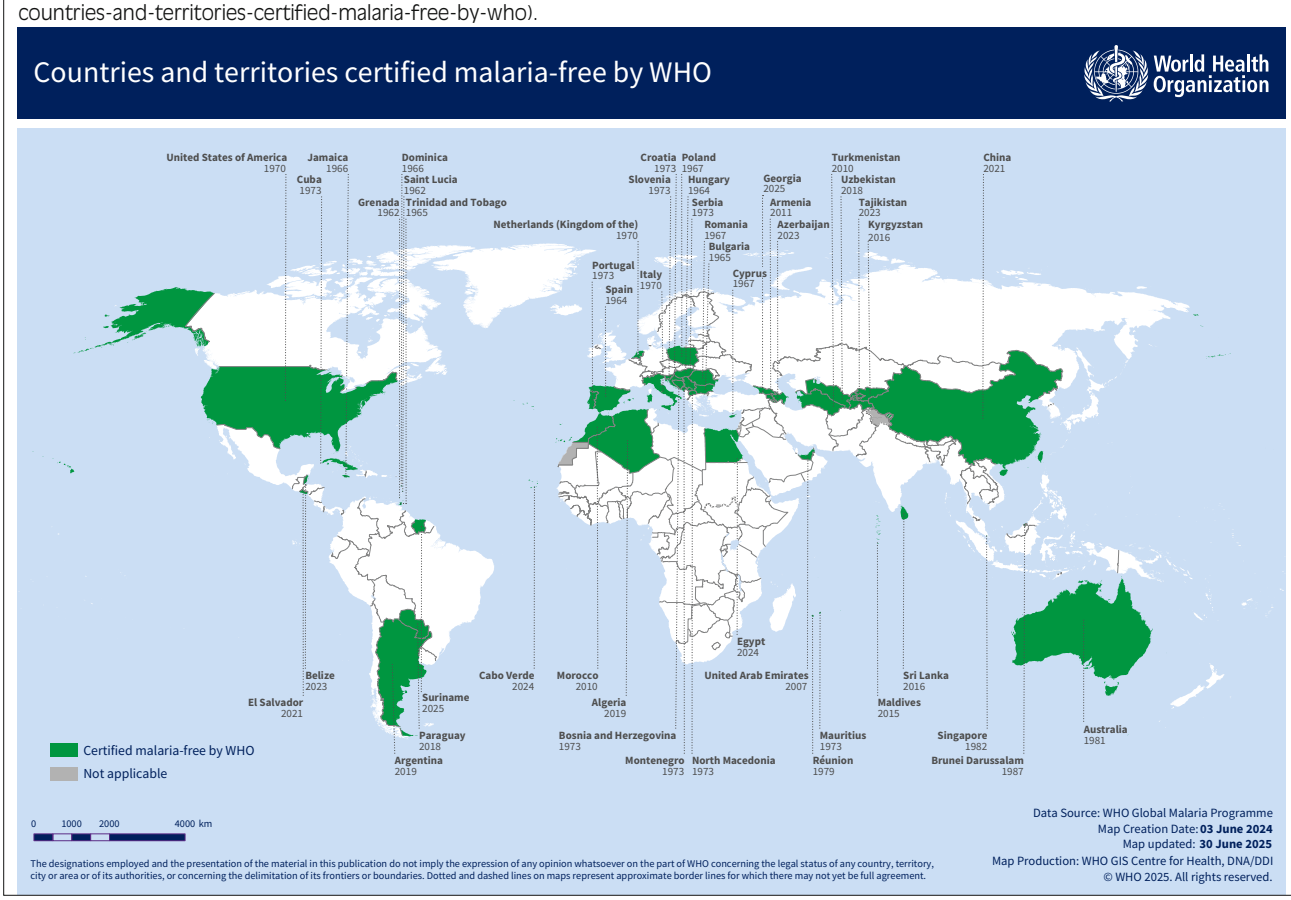
This figure is even more significant in view of the fact that 11 million fewer cases were recorded in 2022. "The WHO African Region continues to carry the heaviest burden of the disease, accounting for an estimated 94% of malaria cases worldwide in 2023" [35].

The five countries with the highest estimated burden of malaria cases in 2023 are listed in the Table I.

Regarding the number of deaths from malaria, the global figure for 2023 is estimated at 597,000, with a mortality rate of 13.7 per 100,000 inhabitants.

The epidemiology of malaria in endemic countries, combined with population movements and international travel, explains the percentage of imported malaria cases in European countries, where malaria has been eradicated

Fig. 5. Countries and territories certified malaria-free by WHO, 2025 (https://www.who.int/teams/global-malaria-programme/elimination/countries-and-territories-certified-malaria-free-by-who).



Tab. I. The five African countries with the highest estimated cases of malaria in 2023 (Data from WHO. World malaria report 2024, available at: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024).

Country	Estimated burden of malaria cases in 2023 (%)
Nigeria	26%
The Democratic Republic of the Congo	13%
Uganda	5%
Ethiopia	4%
Mozambique	4%

since the 1970s. In these countries, too, the disease constitutes a serious threat to individual and public health. In Italy, "a total of 4,372 cases were reported in the years 2017-2023, with an annual average of 624 cases. The most frequently affected category is that of immigrants legally resident in Italy returning from trips to their countries of origin to visit family members" [36].

Based on these data, *"The Global technical strategy for malaria 2016-2030 (GTS) and Sustainable Development Goal 2025 and 2030 targets for malaria morbidity and mortality are unlikely to be met, as the 2023 global malaria incidence is nearly three times higher than needed to reach the target. Although malaria mortality has decreased, it remains more than twice the target level*" [35].

Indeed, the main objective of the World Health Organization is to significantly reduce the incidence and mortality of malaria, achieving by 2030 a reduction of at least 90% in the numbers of cases and deaths recorded in 2015. Specifically, the WHO's 2016-2030 Global Technical Strategy for Malaria aims to eliminate malaria in at least 35 countries by 2030 (Fig. 6).

To achieve these goals, it is essential to reduce malaria transmission by controlling the vector. Indeed, the main measures implemented focus on reducing contact between mosquitoes and humans. However, it should be pointed out that the increasing global temperatures and changes in rainfall patterns create favorable conditions for the proliferation of *Anopheles* mosquitoes, the vector of the *Plasmodium falciparum* parasite.

This means that previously unaffected areas are becoming vulnerable, while endemic areas are seeing an extension of the transmission period and a potential increase in cases.

New avenues are therefore opening up in the fight against malaria, and these could have an even greater impact than the use of DDT in the middle of the 20th century, which enabled us to combat malaria throughout the world [37].

The use of vaccines and new pesticides, but above all the genetic manipulation of mosquitoes, could yield decisive results, bringing us closer to the goal of eradicating the disease.

With regard to vaccines, the turning point came in 2021, when the World Health Organization recommended the first malaria vaccine (RTS,S/AS01, also known as Mosquirix) for children in sub-Saharan Africa and other regions with moderate-to-high transmission of malaria due to *Plasmodium falciparum* [38].

Indeed, children are particularly vulnerable; the WHO estimates that approximately 432,000 children died of malaria in 2023 in Africa alone, the continent most severely affected by this disease.

A critical factor in successful vaccine implementation is community acceptance [39].

A recent literature review has suggested that acceptance of the RTS,S malaria vaccine is high in low- and middle-income countries, with an average acceptance rate of 95.3% [40].

In October 2023, the WHO added a second malaria vaccine, R21/Matrix-M, to the list of pre-qualified vaccines, in order to expand access to malaria prevention through vaccination [41].

Plasmodium falciparum, a parasite that changes shape during its life-cycle

Malaria has been present since ancient time and remains

Fig. 6. Goals, Milestones and Targets for the 2016-2030 Global Technical Strategy for Malaria (WHO. Global technical strategy for malaria 2016-2030, 2021 update, 19 July 2021 (https://www.who.int/publications/i/item/9789240031357).

AIM & GTS for Malaria Joint Vision: *a world free of malaria*			
Goals	Milestones		Targets
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent resurgence of malaria in all countries that are malaria-free	Resurgence prevented	Resurgence prevented	Resurgence prevented

a major global health problem in developing countries. Human malaria is an ancient tropical disease caused by infection with protozoan parasites belonging to the genus *Plasmodium* and is transmitted by female mosquitoes of the genus Anopheles.

Although malaria has been known since ancient times, the protozoan responsible for the disease was identified in the blood of affected individuals only in 1880.

Among the various species of *Plasmodium* parasites, four are the most widespread. The most dangerous, however, is *Plasmodium falciparum*, which is responsible for most cases of human malaria worldwide (80%) and is deeply entrenched in tropical Africa [42] and is responsible for the highest mortality rate among infected subjects. *Plasmodium falciparum* is the etiological agent of malaria tropica, the leading cause of death due to a vector-borne infectious disease, claiming 0.5 million lives every year [43].

It lives and reproduces, in different stages, in human blood and in some species of mosquitoes belonging to the genus *Anopheles*.

When the mosquito bites a human, it inoculates sporozoites, the infectious forms of *Plasmodium*, which are able to evade the immune system.

The parasite develops inside the human organism. First, it reaches the liver, where it invades the hepatocytes. There, it multiplies by producing merozoites (pre-erythrocytic phase). It then infects the red blood cells, multiplying further (erythrocytic phase).

After a few cycles of asexual development, the *Plasmodium* produces gametocytes, sexuate forms of the parasite that remain in the blood of sick persons for a few weeks and are thus able to infect other mosquitoes that bite them.

The different gene expression of *Plasmodium* in different phases of its life-cycle [44] and the considerable polymorphism of its antigens constitute a major problem from the epidemiological standpoint; the different variants enable the parasite to evade the human immune system, making it difficult to target with vaccines and treatments.

While the vaccines currently in use block the replication of the parasite in the pre-erythrocytic phase, the latest studies aim to use the genetically attenuated whole sporozoite.

Is genetic mutation the solution to malaria?

In the early 2000s, genetic engineering techniques began to be used in an attempt to combat malaria. Genetic engineering may enable us to modify entire populations of mosquitoes and to control the transmission of malaria. One of the most futuristic techniques being studied involves modifying the DNA of mosquitoes in order to render them sterile. Some of the studies being conducted in this area aim to target a very specific gene in the mosquito genome.

The technology called "gene drive" enables the genome of an organism to be modified through the use of a "drive", usually an enzyme, that cuts the DNA at the genes involved in the transmission of the malaria parasite [45]. This mutation renders females sterile, as it prevents the formation of eggs. It has been predicted that introducing genetically modified mosquitoes into a population would halt its reproductive capacity within a few generations, resulting in the collapse of the population [46, 47].

This innovative genetic engineering technique may therefore be able to eliminate malaria-carrying mosquitoes permanently.

Another recent study has led scientists to create a genetically weakened version of the parasite, called GA2, which is unable to cause disease but capable of eliciting a robust immune response. When a genetically modified mosquito bites a human, the modified parasite reaches the liver, where, however, it develops more slowly than an unmodified *Plasmodium*.

This delay allows the immune system to recognize and fight the parasite, preparing the body to repel any future infections [48].

These and other possibilities may prove to be alternative preventive strategies that have the potential to improve protection against malaria and offer great hope of a definitive solution to this disease.

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

Authors' contributions

DO: conceived the study; DO & MM: designed the study; drafted the manuscript; performed a search of the literature; revised the manuscript; conceptualization and methodology; investigation and data curation; original draft preparation; review; editing. All authors have read and approved the latest version of the paper for publication.

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Infectious diseases

Delivering physical rehabilitation services during the COVID-19 pandemic in Iran: Common challenges and potential solutions for future pandemics

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Keywords

Physical Rehabilitation, COVID-19, Pandemics, Health Policy, Qualitative study, Iran.

Summary

The COVID-19 pandemic affected people with disabilities in different aspects, including their access to physical rehabilitation (PR). Despite a significant global surge in the need for PR, it has not been prioritized and is under-resourced, even in the non-COVID era, in many countries. This study aimed to explore the challenges of delivering PR services during the COVID-19 pandemic in Iran and potential solutions to these challenges. This qualitative study was done using a thematic approach from November 2023 to March 2024 in Iran. 45 PR professionals and faculty members from three fields—physiotherapy, occupational therapy, and orthotics and prosthetics—were interviewed in a semi-structured approach. Data analysis was done using Braun and Clarke's thematic analysis approach. The five control knobs (organization, regulation, financing, payment, and behavior) were used to study the challenges and proposed solutions. The main identified challenges included Iran's healthcare system's lack of preparedness, deficient infrastructure, limited remote rehabilitation options, restriction of in-person visits, lack of clinical guidelines, ambiguous pricing for telerehabilitation, financial hardships stemming from the pandemic, insufficient government support, reliance on out-of-pocket (OOP), patients' reluctance to pay for online services, delayed compensation for PR professionals, mental distress experienced by patients and service providers, resistance to new service modalities, and inadequate digital literacy. The key solutions included strengthening telerehabilitation infrastructure, developing clear clinical guidelines, increasing government financial support, improving payment structures, and fostering behavioral changes through increased awareness. The findings of this study underscore the importance of proactive planning, intersectoral collaboration, and the integration of PR services within the healthcare framework. The suggested solutions can inform policymakers to enhance the preparedness and responsiveness of health systems to future crises.

Introduction

On March 11, 2020, the World Health Organization (WHO) characterized the outbreak of SARS-CoV-2, COVID-19, as a pandemic [1]. Tragically, numerous individuals succumbed to the virus, while many others grappled with long-term physical impairments stemming from their encounter with COVID-19 [2]. The enforced isolation, coupled with the loss of loved ones and the pervasive uncertainty surrounding the virus, gave rise to a surge in psychological distress and mental health challenges. Moreover, the ripple effects of the pandemic extended far beyond its direct health impacts [3]. Governments around the world responded with a range of policies aimed at containing the spread of the virus, including the closure of non-essential businesses, the promotion of remote work, and the implementation of mask mandates and social distancing protocols. Measures such as quarantine, social distancing, and travel restrictions reshaped daily life for billions of people, leading to profound disruptions in social interactions and economic activities [4-6].

Physical rehabilitation (PR) services effectively improve the disability of individuals with various disease conditions [7]. During the COVID-19 pandemic, the field of PR also faced challenges. For example, COVID-19 affected people with disabilities in different aspects, including their access to PR services [8, 9]. The pandemic disrupted or limited their ability to communicate with healthcare professionals and access multidisciplinary PR services. There was widespread concern that rehabilitative treatments might not be available if the pandemic worsened or new strains of COVID-19 emerged [10]. Many people

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with chronic diseases like stroke and cerebral palsy find that the absence of PR benefits heightens their risk of disease progression [11]. During the COVID-19 pandemic, patients' access to essential PR services was limited, resulting in secondary injuries, adverse outcomes, exacerbating functional limitations, and hindering recovery [2].

Providing sub-acute and non-emergency PR services during a pandemic presents significant challenges in maintaining a safe environment for both clients and health service providers. However, offering PR services at different levels is crucial, as these services are essential in optimizing physical and cognitive performance while reducing disability [12]. Even in the non-COVID era [13], many countries have neglected and under-resourced PR despite a significant global surge in its need. Iran had a high incidence and mortality rate of COVID-19 [14], indicating the challenges of disease control in the country. Before the emergence of the COVID-19 pandemic, Iran's PR sector was already facing multi-layered challenges [15, 16]. The pandemic posed additional challenges to the delivery of PR services. Major changes have occurred in healthcare delivery, shifting many services from in-person to remote options like telemedicine and telerehabilitation. This shift involved using video calls and medical care apps more widely, as well as an increase in home services [17].

However, the reliance on clinical equipment presented challenges for therapists and clients, necessitating the continuation of some in-person services. Understanding these challenges is critical to finding solutions to overcome them. Given the rapid and far-reaching impact of COVID-19 on global healthcare systems, it has become increasingly evident that comprehensive and adaptable strategies are essential to ensure timely access to PR services, especially for individuals with complex needs and limited functional abilities [8]. Timely access to PR services is crucial, and there is a fundamental need for widely applicable recommendations and policies. In light of the challenges posed by COVID-19, there is an urgent need to develop robust and adaptable PR policies and practices that can withstand the complexities of future pandemics [18]. This will help ensure that PR care for individuals with complex needs and functional limitations is less disrupted during future pandemics.

Some aspects of COVID-19 rehabilitation challenges in Iran are still unclear. PR specialists such as physical therapists, occupational therapists, and orthotists/prosthetists faced many challenges and problems during the pandemic. Therefore, this study was conducted to explore the common challenges faced by PR practitioners and faculty members in delivering PR services in Iran during the COVID-19 pandemic. Also, potential solutions were explored, hoping they could aid in providing more appropriate PR services under similar disruptive conditions in the future.

Methods

Study design

This qualitative study was carried out using a thematic approach from November 2023 to March 2024 in Iran. This research method provides the necessary opportunity to gain a deeper understanding of the participants' perspectives on a specific issue. The practitioners and faculty members of three fields of PR (physiotherapy, occupational therapy, and orthotics and prosthetics) were selected to attend semi-structured interviews. The Critical Appraisal Skills Programme (CASP) checklist for qualitative studies [19] and the Standards for Reporting Qualitative Research (SRQR) criteria [20] were considered to ensure methodological and reporting quality, respectively.

Sampling strategy

The sample selection process started with purposive sampling and continued with snowball sampling. We tried to include samples from different ages, genders, educational levels, specialties, job status, and employment types to ensure maximum diversity. In order to find potential samples, virtual networks such as LinkedIn and Instagram were used, as well as Ministry of Health and Medical Education databases like the Medical Council of the Islamic Republic of Iran and the Iranian Scientometric Information Database. According to the inclusion criteria, practitioners with at least four years of clinical experience and faculty members with at least three years of academic experience in the three fields of physiotherapy, occupational therapy, and orthotics and prosthetics were selected. After the initial contact, an invitation containing the informed consent form and general information related to the research was sent to her/him via email or WhatsApp. At the beginning of each interview, the interviewer verbally provided information related to the research to the interviewee, and after receiving her/his consent, they started the interview. The informed consent form stated that the interviewee could withdraw from the study at any stage. The sampling process continued until no new findings were added and saturation was reached. The last four interviews with duplicate data were considered to ensure data saturation.

Data Collection

Three authors (PM, TA, and AT) conducted individual semi-structured interviews in both online and written formats. Each interviewer conducted interviews in one of the fields (physiotherapy, occupational therapy, or orthotics/prosthetics). We used an interview guide containing open questions (Tab. I) to better manage and direct the interview flow. When conducting an online interview proved unfeasible, we sent a list of open-ended questions and probes to the participants, encouraging them to share their detailed experiences. Based on the participants' feedback, we revised the initial interview questions to enhance transparency. We collected data during the interview sessions using a digital audio

Tab. I. Interview guide including open-ended questions

Describe your experience of providing rehabilitation services during the COVID-19 pandemic.
In your opinion, what were the most significant challenges and obstacles in providing rehabilitation services during the COVID-19 pandemic? Describe your experiences.
Have there been any obstacles regarding maintaining motivation and patient participation in remote rehabilitation sessions, and how have you addressed these issues?
What challenges did you face in obtaining the necessary equipment or technology for providing rehabilitation services during the pandemic?
Are there any educational or professional development opportunities that have helped you adapt to the challenges related to the pandemic and improve the delivery of rehabilitation services?
How have financial constraints or budget limitations during the pandemic affected your ability to provide rehabilitation services, and how have you managed these challenges?
Have you taken any measures to expand access to rehabilitation services for disadvantaged or vulnerable populations during the pandemic, and what have been the results?
Are you aware of experiences from other countries in providing rehabilitation services during the COVID-19 pandemic? If possible, provide examples of their approaches.
What are your suggestions for improving the delivery of rehabilitation services during pandemics like COVID-19 and in the post-COVID-19 era?

recorder and note-taking. After each interview, we wrote the recorded files and saved them in Office Word.

Data Analysis

The Braun and Clarke's thematic analysis approach was used to analyze the collected data [21]. The six steps of this approach are: (1) familiarising oneself with the collected data; (2) identifying the initial codes; (3) establishing the themes; (4) reviewing and revising the themes; (5) naming the emerging themes; and (6) reporting the findings [22]. Three authors (PM, SSH, and TA) analyzed the data. In this regard, written texts were independently reviewed and initial coding was done. Then, the identified codes were sorted and sub-themes were formed. In final, the emerged sub-themes were assigned to each component of the five control knobs framework (organization, regulation, financing, payment, and behavior) [23, 24]. Any disagreements at this stage were resolved through discussion, and when necessary, by the participation of a third expert (MB).

Rigor and Trustworthiness

Researchers use various strategies to ensure the rigor and trustworthiness of qualitative studies [25]. Guba and Lincoln have recommended five criteria in this regard: dependability, credibility, transferability, authenticity, and confirmability [26, 27]. The study adopted the following approaches to meet these criteria: (1) involving researchers with different executive and scientific backgrounds (dependability); (2) monitoring and assessing the findings by peers (credibility); (3) aiming for the greatest diversity in recruited samples (transferability); (4) considering direct quotes from almost all participants (authenticity); and (5) evaluating the findings by involved individuals (confirmability).

Results

To gather data on challenges in delivering PR care during the COVID-19 pandemic and explore potential solutions using a framework with five control knobs, we interviewed 45 professionals in PR, including fifteen physiotherapists, fifteen occupational therapists, and fifteen orthotists and prosthetists (Tab. II). We present the identified challenges and solutions (Tabs. II, IV), aligned with each dimension of the framework, alongside direct quotes from participants.

Challenges

Organization

In our interviews, some participants were concerned about the fragility of the healthcare system. This fragility becomes especially pronounced when we consider the delivery of PR services during crises like pandemics. The system's lack of resilience was a formidable barrier, hindering our ability to effectively tackle healthcare emergencies, as our interviewees stressed.

> *"Iran's lack of a resilient health system has rendered it unable to respond well to threats such as pandemics. This is why the* PR *services are not well organized for crises"* [15].

One challenge was the lack of PR experts in Iran's health policy-making circles. This sidelines the development of PR services and undermines their importance within our healthcare framework, as some participants have noted.

> *"Policy-making and decision-making processes within Iran's health system do not significantly involve PR specialists. This often leads to the neglect of PR services"* [21].

The interviewees pointed out the challenges stemming from inadequate collaboration among providers of PR services. This lack of cooperation complicates service delivery and hampers the integration of rehabilitation care into the healthcare system.

> *"There is no acceptable cooperation and coordination between the responsible institutions in the field of providing* PR *services"* [19].

Our interviews also revealed a glaring oversight: the neglect of deprived regions. This oversight exacerbates existing disparities in healthcare access and outcomes, leaving vulnerable populations even more marginalized.

> *"No specific action was taken to improve the use of PR services during the COVID-19 pandemic in deprived areas"* [02].

Additionally, our participants emphasized the strain that workforce shortages cause in effectively delivering rehabilitation services. This shortage not only burdens existing staff, but it also disrupts service provision when personnel need to take leave, be it for illness or other reasons.

"Another problem was that when someone [the provider] got sick and went on leave, there was no one to support us" [17].

Another poignant issue brought up was the heavy workload faced by healthcare professionals delivering PR services. This workload not only taxes our personnel but also takes a toll on their mental well-being, leading to serious consequences.

"Some of the medical staff committed suicide due to high work and psychological pressure" [19].

Linked to this is the lack of job stability among PR sector workers, as pointed out by our participants. This instability, marked by uncertain contract renewals, undermines morale and dedication, ultimately affecting the quality and continuity of PR services.

"Some providers did not have their contract renewed by the hospital despite their hard work" [31].

Shifting gears, our interviews also shed light on the challenges posed by inadequate internet infrastructure. This infrastructure gap not only hampers communication but also limits the adoption of telehealth solutions, critical in delivering remote PR services.

"The main problem was the low speed of the Internet, which created a challenge" [33].

Moreover, participants highlighted the financial burden posed by the high cost of internet access. This burden, borne by both healthcare providers and recipients, further restricts access to telehealth solutions, impeding the reach of PR interventions.

"The cost of the Internet was a challenge for both the therapist and the service recipient" [43].

Transportation emerged as another significant barrier to accessing PR services, particularly during the pandemic. The challenges of commuting and accessing physical services exacerbate the difficulties faced by both providers and patients, hampering the delivery and receipt of essential care.

"During this pandemic, commuting and benefiting from physical services had become difficult" [04].

"The most important challenge was the patients' transportation" [05].

Our interviews also underscored the frustration stemming from delays in obtaining the COVID-19 vaccine. These delays not only increase the risk of infection among healthcare providers but also prolong the hiatus in essential services, further burdening our healthcare system.

"On the other hand, it took a long time to get the vaccine" [31].

Furthermore, the restriction on face-to-face visits emerged as a significant challenge in providing PR services. This limitation not only complicates assessments and interventions, but also impedes progress monitoring, particularly for vulnerable populations like children.

"Not being able to see patients directly was annoying" [01].

"Limited physical interaction was the biggest problem that arose. In fact, it made it difficult to do physical exercises, which led to children's regression" [44].

Similarly, our participants expressed dissatisfaction with the limitations of home-based care. The inability of therapists to conduct home visits hampers the delivery of personalized interventions, impacting the effectiveness of care provision.

"Many people were not satisfied that therapists visited their homes" [01].

Moreover, inadequate communication infrastructure posed another hurdle for healthcare providers delivering PR services. The lack of essential equipment like smartphones or laptops hinders effective coordination among therapists, disrupting the continuity of care.

"Therapists themselves had the challenge of not having access to equipment such as smartphones or laptops" [31].

Additionally, concerns were raised about the clinical environment for delivering PR services, especially during the pandemic. Issues like improper ventilation and the need for protective gear further complicate service delivery, affecting the quality of care and patient experience.

"It was much more difficult to work because the clinic spaces were not properly ventilated, and we had to work with masks and special covers" [38].

Our interviews also underscored concerns about the sustainability of PR services post-pandemic. The lack of continuity in service delivery creates gaps in care provision, hindering long-term recovery efforts.

"Unfortunately, these services were not continued after the COVID-19 pandemic" [31].

Furthermore, the inadequate availability of personal protective equipment (PPE) during the early stages of the pandemic raised significant concerns. The scarcity of essential protective gear not only jeopardizes healthcare providers' safety, but also compromises PR service delivery.

"At the start of the COVID-19 pandemic, masks and disinfectants were scarce, which was concerning" [16].

Similarly, our participants expressed concerns about the poor quality of the available PPE. Substandard equipment not only compromises safety but also impacts comfort and mobility, affecting the quality of care delivered.

"The quality of the hospital gowns was awful and limited the therapist's range of motion" [31].

Moreover, the exorbitant cost of PPE emerged as another challenge. The sharp rise in prices places a significant financial strain on healthcare providers and facilities, limiting their ability to procure essential protective gear.

"The price of latex gloves had increased about 10 times" [18].

The continuation of the result section have been inserted in Supplementary file 1.

Discussion

The findings from this study provide valuable insights into the multifaceted challenges faced by PR professionals during the COVID-19 pandemic.

Tab. II. Characteristics of included participants.

Name (ID)	Gender	Age	Educational level	Profession	Job (Clinician/faculty member)	Job status (part- or full-time)		Clinical experience	Academic experience	Job location (city)	Employment (private, government, NGO, etc.)	Type of Unit (Acute, Sub-acute, Emergency, etc.)	Vaccination status
01	Female	54 year	PhD	Orthotics & Prosthetics	Faculty Member	Full-time		28 year	25 year	Tehran	Government	Subacute	Done
02	Male	59 year	PhD	Orthotics & Prosthetics	Faculty Member	Full-time		30 year	20 year	Tehran	Government	Subacute	Done
03	Male	48 year	PhD	Orthotics & Prosthetics	Faculty Member	Full-time		27 year	10 year	Tehran	Government	Subacute	Done
04	Male	48 year	PhD	Orthotics & Prosthetics	Faculty Member	Full-time		18 year	18 year	Tehran	Government	Subacute	Done
05	Male	43 year	PhD	Orthotics & Prosthetics	Faculty Member	Full-time		15 year	14 year	Tehran	Government	Subacute	Done
06	Male	49 year	Bachelor	Orthotics & Prosthetics	Clinician	Part time		20 year	-	Tehran	Government	Subacute	Done
07	Male	34 year	Master	Orthotics & Prosthetics	Clinician	Full-time		10 year	-	Tehran Semnan	Private	Subacute	Done
08	Female	27 year	Bachelor	Orthotics & Prosthetics	Clinician	Part time		4 year	-	Rafsanjan	Government	Subacute	Done
09	Male	57 year	PhD	Orthotics & Prosthetics	Clinician	Full-time		29 year	-	Tehran	Private	Subacute	Done
10	Male	31 year	Bachelor	Orthotics & Prosthetics	Clinician	Full-time		8 year	-	Tehran	Government	Subacute	Done
11	Male	31 year	Master	Orthotics & Prosthetics	Clinician	Full-time		8 year	-	Tehran	Government	Subacute	Done
12	Female	27 year	Bachelor	Orthotics & Prosthetics	Clinician	Part time		5 year	-	Tehran	Government	Subacute	Done
13	Female	30 year	Bachelor	Orthotics & Prosthetics	Clinician	Part time		8 year	-	Tehran	Government	Subacute	Done
14	Female	25 year	Bachelor	Orthotics & Prosthetics	Clinician	Part time		6 year	-	Tehran	Private	Subacute	Done
15	Female	26 year	Bachelor	Orthotics & Prosthetics	Clinician	Part time		6 year	-	Tehran	Private	Subacute	Done
16	Female	33 year	PhD	Physiotherapist	Faculty member of the University of Rehabilitation Science and Social Welfare	Full-time		11 years	7 years	Tehran, University of Rehabilitation Science and Social Welfare	Commitment to service	Clinic	Done
17	Female	34 year	Bachelor	Physiotherapist	Clinician	Full-time		9 years	-	Qom	Private contract	Clinic	Done
18	Female	38 year	Professional Doctorate	Physiotherapist	Clinician	Full-time		16 years	-	Tehran	Employer	Clinic	Done
19	Male	57 year	Master	Physiotherapist	Head of Physiotherapy Department in Shiraz Oil industry, Chairman of the Physiotherapy association, Board member of the medical council, Author of the physiotherapy service standards in COVID-19, Clinician	Full-time		33 years	Presenter of articles	Shiraz	Government	Health and Treatment of Oil Industry	Done
20	Male	35 year	PhD	Physiotherapist	Clinician	Full-time		12 years	7 years	Tehran	Private	Clinic	-
21	Male	29 year	PhD	Physiotherapist	Clinician, University lecturer	Full-time		7 years	4 years	Tehran	Government	University, Clinic, Hospital (Orthopedics)	Done
22	Male	42 year	Master	Physiotherapist	Clinician	Full-time		18 years	3 years	Mashhad	Government	Mashhad university hospital (Dr. Sheikh, Hemophilia and Thalassemia patients)	Done
23	Female	31 year	PhD	Physiotherapist	Clinician	Part-time		8 years	4 years	Shiraz	Government	Rehabilitation Faculty Clinic	Done

Tab. II *(follows).* Characteristics of included participants.

Name (ID)	Gender	Age	Educational level	Profession	Job (Clinician/faculty member)	Job status (part- or full-time)		Clinical experience	Academic experience	Job location (city)	Employment (private, government, NGO, etc.)	Type of Unit (Acute, Sub-acute, Emergency, etc.)	Vaccination status
24	Male	46 year	Professional Doctorate in Physiotherapy	Physiotherapist	Clinician	Full-time		23 years	10 years	United States, Maryland State	Private	Clinic	Done
25	Male	62 year	PhD	Physiotherapist	Faculty member of the Jundishapur University	Full-time		34 years	25 years	Ahvaz	Government	Rehabilitation Faculty Clinic	Done
26	Male	31 year	Bachelor	Physiotherapist	Clinician	Full-time		5 years	-	Mashhad	Government	Imam Reza Hospital, University Clinic (Inpatients from all departments and Outpatient), Transplant Hospital	Done
27	Male	35 year	Master	Physiotherapist	Clinician	Full-time		10 years	-	Yazd	Government & Private	Hospital (Inpatient & Outpatient), Clinic	Done
28	Male	38 year	PhD	Physiotherapist	Clinician & Attending Physiotherapist	Full-time		16 years	4 years	Tehran	Contractual, Private	Hospital (Inpatient & Outpatient), Clinic	Done
29	Male	25 year	Bachelor	Physiotherapist	Clinician	Evening shift every day (7 hours)		4 years	-	Tehran	Government	Hospital (Inpatient & Outpatient)	Done
30	Male	41 year	Professional Doctorate in Physiotherapy	Physiotherapist	Clinician	Full-time		18 years	15 years	Zahedan	Government	Ali Ibn Abi Taleb Hospital (Responsible for the Rehabilitation Department of the Hospital)	Done
31	Female	29 year	PhD	Occupational therapist	Faculty Member, Tabriz university	Full-time		6 year	4 year	Tabriz	Government	University, Hospital (Inpatient & Outpatient), Acute, Neurology	Done
32	Female	39 year	PhD	Occupational therapist	Faculty Member, Shahid Beheshti University	Full-time		12 year	6 year	Tehran	Government	University, Clinic, Subacute, Neurology	Done
33	Male	35 year	PhD	Occupational therapist	Faculty Member, Tabriz university	Full-time		12 year	6 year	Tabriz	Government	University, Clinic, Hospital (Neurology & orthopedy)	Done
34	Male	38 year	PhD	Occupational therapist	Faculty Member, Tehran university	Full-time		15 year	6 year	Tehran	Government	Neurology, Subacute	Done
35	Male	32year	Master	Occupational therapist	Faculty Member, Tabriz university, Clinician	Full-time		8 year	4 year	Tabriz	Government, Private	Subacute	Done
36	Female	30 year	Master	Occupational therapist	Clinician	Full-time		7 year	-	Tehran	Private	Subacute, Neurology & Mental	Done
37	Female	31 year	Bachelor	Occupational therapist	Clinician	Full-time		8 year	-	Tabriz	Private	Subacute, Neurology & Mental	Done
38	Female	29 year	Master	Occupational therapist	Clinician	Full-Time		6 year	-	Tehran	Private	Subacute,Mental	Done
39	Female	30 year	Bachelor	Occupational therapist	Clinician	Full-time		7 year	-	Urmia	Private	Subacute	Done
40	Male	32 year	Bachelor	Occupational therapist	Clinician	Full-time		8 year	-	Tabriz	Private	Subacute, Pediatric occupational therapy	Done
41	Female	28 year	Bachelor	Occupational therapist	Clinician, Imam Reza hospital	Full-time		6 year	-	Tabriz	Government	Acute	Done
42	Male	32 year	Bachelor	Occupational therapist	Clinician	Part time		8 year	-	Karaj	Private	Subacute, Neurology	Done
43	Female	32 year	Bachelor	Occupational therapist	Clinician	Part time		5 year	-	Tehran	Private	Subacute, Neurology & Mental	Done
44	Male	31 year	Bachelor	Occupational therapist	Clinician	Full-time		8 year	-	Sanandaj	Private	Subacute, Neurology & Mental	Done
45	Female	30 year	Bachelor	Occupational therapist	Clinician	Full-time		5 year	-	Rasht	Private	Subacute, Neurology & Mental	Done

Challenges

The most commonly cited challenges hindering the effective delivery of PR services are discussed in five dimensions:

At the organizational level, one of the main challenges to PR services during the COVID-19 period was the insufficient preparedness of Iran's health system to respond appropriately to the specific conditions that arose. This situation negatively impacted the PR of people with disabilities, many of whom relied on consistent PR for chronic conditions. In addition, the COVID-19 infection added a significant number of patients to inpatient and outpatient rehabilitation settings, which were already grappling with significant challenges in providing services for their non-COVID clients. Many participants cited inadequate PPE, including basic items such as masks, as evidence of unpreparedness, especially in the early stages of the pandemic. The high cost and subpar quality of some available PPE posed additional challenges.

Participants repeatedly mentioned slow internet as a significant obstacle to replacing face-to-face PR visits with online visits. Deficient prerequisite telecommunication equipment aggravated the problem. The limited remote PR options hampered access to care, especially for those in remote or underserved areas, exacerbating disparities in healthcare access and outcomes. On the other hand, the processes of assessment and provision of certain therapeutic interventions were complicated due to the restriction of face-to-face appointments. Similarly, in PR educational settings, numerous educational programs encountered significant challenges and necessitated a transition to alternative programs [28]. The absence of PR experts in health policy-making further marginalized the sector, contributing to the neglect of PR needs.

Overall, the participants indicated that Iran's healthcare system lacked resilience and was fragile. They pointed out various aspects of the system's inadequate preparedness to respond appropriately to the pandemic. Lack of preparation was not unique to Iran, and although some countries were able to adopt successful PR approaches, most governments' reactions to the crisis were late and ill-organized [2, 29]. Learning from these experiences is important for getting better prepared.

Regulatory challenges centered around the absence of comprehensive clinical practice guidelines and ambiguity in pricing structures for telerehabilitation. Practitioners have long used clinical guidelines to guide healthcare decisions for specific clinical circumstances [30]. Unprecedented challenges presented during the COVID-19 era hampered healthcare providers' ability to deliver consistent and evidence-based care and contributed to uncertainty and variability in service provision. This impact may lead to future effects such as reduced functioning and increased caregiving burden, resulting in decreased participation of individuals with disabilities in society [31]. Determining the tariff for healthcare services in Iran has been a controversial process that has faced criticism from many stakeholders [32]. Clear tariffs help regulate the relationship between provider and recipient of services. The vagueness of pricing for alternative methods of providing PR services during the COVID-19 pandemic could jeopardize this relationship and negatively impact the treatment process.

Financial hardships rose after the COVID-19 pandemic further exacerbated access to PR. The pandemic significantly impacted economic conditions. Studies have shown that the pandemic disproportionately affected economically disadvantaged groups [33, 34]. In this scenario, individuals with disabilities from lower socioeconomic backgrounds faced increased challenges in accessing PR services. Many patients need long-term PR therapies, and some PR services, such as prostheses, are expensive. The majority of PR services in Iran are financed out-of-pocket (OOP) [16]. Limited access to PR may exacerbate the condition and predispose the patient to more severe financial hardship. To prevent and break the vicious cycle of chronic disease and poverty, financial support should be considered [35]. As a result, the lack of government support, a frequently cited challenge, not only hindered the delivery of PR to those in need, but also potentially had long-term socioeconomic and health implications. Iranian healthcare has identified insufficient financial support from the government as a challenge in fighting the COVID-19 pandemic [36].

Participants pointed out payment difficulties. Patients' reluctance to pay for online services, in addition to causing financial issues, impeded the adoption of telerehabilitation solutions during the COVID-19 pandemic. Inadequate and delayed payments for therapists during the pandemic affected their financial well-being, increasing their worries and feelings of frustration. This reflects a broader failure to recognize the value of their contributions to healthcare delivery. Researchers have detailed the influences of payment methods and financial and nonfinancial incentives on the practice of healthcare professionals [37-39].

The participants most frequently cited challenges related to behavioral factors. Many participants indicated the mental pressures of the COVID-19 pandemic on both healthcare professionals and patients. Participants highlighted anxiety about the virus's transmission as a serious concern. These findings are consistent with studies that have emphasised the importance of addressing the psychological consequences of the pandemic [40-42]. Timely psychological counselling is crucial for ensuring the well-being of those involved in PR services, and overcoming the anxiety of contracting the infection is essential to ensuring continued access to necessary care. Resistance to adopting new service modalities, particularly among older therapists and patients, had a significant impact on the use and provision of PR services. Researchers have discussed negative attitudes towards telerehabilitation and low levels of digital literacy, particularly in older people, as barriers to its implementation [43, 44]. We should address these obstacles to foster trust and acceptance of innovative healthcare delivery approaches.

Tab. III. Identified challenges in delivering physical rehabilitation services during the COVID-19 pandemic in Iran.

Main themes	Challenges	Direct quotes	Participants' ID
Organization	Lack of a resilient health system	"Iran's lack of a resilient health system has made it unable to respond well to threats such as pandemics.» This is why the rehabilitation services are not well organized for crises." [15]	15, 19, 34
	Non-involving of rehabilitation experts in policy-making	"Policy-making and decision-making processes within Iran's health system do not significantly involve rehabilitation specialists.» This often leads to the neglect of rehabilitation services." [21]	17, 21, 40
	Lack of inter-sectoral collaboration	"There is no acceptable cooperation and coordination between the responsible institutions in the field of providing rehabilitation services." [19]	19, 23
	Lack of attention to deprived regions	"No specific action was taken to improve the use of rehabilitation services during the COVID-19 pandemic in deprived areas." [02]	02, 07, 21, 31, 41
	Inadequate workforce	"Another problem was that when someone [the provider] got sick and went on leave, there was no one to support us." [17]	17, 31
	High workload	"Some of the medical staff committed suicide due to high work and psychological pressure." [19]	19, 21, 31, 34
	Lack of job stability	"Some providers did not have their contract renewed by the hospital despite their hard work." [31]	31
	Weak internet	"The main problem was the low speed of the Internet, which created a challenge." [33]	01, 02, 16, 33, 34, 35, 37, 38, 39, 40, 42, 43
	High cost of internet	"The cost of the Internet was a challenge for both the therapist and the service recipient." [43]	43
	Transportation challenges	"During this pandemic, commuting and benefiting from physical services had become difficult." [04] "The most important challenge was the patients' transportation." [05]	04, 05, 32, 39, 42
	Delay in vaccination	"On the other hand, it took a long time to get the vaccine." [31]	31
	Limitation of face-to-face visits	"Not being able to see patients directly was annoying." [01] "Limited physical interaction was the biggest problem that arose. In fact, it made it difficult to do physical exercises, which led to children's regression." [44]	01, 03, 04, 05, 07, 09, 11, 14, 24, 26, 37, 38, 44
	Limitation of home-based care	"Many people were not satisfied that therapists visited their homes." [01]	01, 36
	Lack of communication infrastructure	"Therapists themselves had the challenge of not having access to equipment such as smartphones or laptops." [31]	31, 34, 36, 37, 45
	Inappropriate clinical environment	"It was much more difficult to work because the clinic spaces were not properly ventilated, and we had to work with masks and special covers." [38]	23, 32, 38
	Lack of sustainable service delivery	"Unfortunately, the COVID-19 pandemic prevented the continuation of these services." [31]	31
	Inadequate PPE	"At the start of the COVID-19 pandemic, masks and disinfectants were scarce, which was concerning." [16]	01, 02, 12, 16, 19, 20, 22, 23, 24, 25, 28, 29, 30
	Poor quality of available PPE	"The quality of the hospital gowns was awful and limited the therapist's range of motion." [31]	02, 22, 28, 31
	High cost of PPE	"The price of latex gloves had increased about 10 times." [18]	05, 18, 21, 28, 30
	Inadequate attention to rehabilitation practitioners	"Physiotherapists received none of the incentives offered to other health system employees during COVID-19." [22]	22, 26, 28, 30
	Lack of in-service training	"Special educational opportunities were not available at that time." [45]	04, 10, 11, 18, 21, 33, 34, 45
	Clinical education issues	"In my opinion, the COVID-19 pandemic negatively impacted the students present during that period. The treatment method was significantly different and the patient count was significantly lower." [21]	01, 21
	Lack of effective telerehabilitation	"There are practically no telerehabilitation services in Iran." [06]	02, 06, 11, 15, 24, 30, 33, 39, 41
	Limited access to raw materials	"At times, we encountered difficulties when purchasing prosthetic parts for patients, as the process of importing goods and customs unintentionally encountered some issues due to the impact of the crisis. However, these issues were not severe or unmanageable." [02]	02, 03, 05, 09
	Lack of attention to private sector	"The support during the COVID-19 era was only for government centers, and private centers were not given support." [19]	19

▶

Tab. III *(follows).* Identified challenges in delivering physical rehabilitation services during the COVID-19 pandemic in Iran.

Main themes	Challenges	Direct quotes	Participants' ID
Regulation	Lack of comprehensive clinical guidelines	"There was no specific guideline for the COVID-19 era, and it was mostly the experience of the providers." [35]	19, 27, 35, 42
	Unclearing of online service tariffs	"The tariff for providing rehabilitation services online was not very clear." [35]	35
	Unrealistic tariffs of rehabilitation services	"Unfortunately, the tariff of many rehabilitation services is not proportional to the amount of work done." [19]	19
Financing	Financial hardships	"Financial problems posed another obstacle for the patients, as they had fallen financially, and many of them experienced job disruptions, making it difficult for them to perform occupational therapy and pay the fees." [31] "Some people had financial problems and could not afford a smartphone, especially in the surrounding cities, where they used to text and explain the exercises to these clients." [37]	01, 04, 17, 18, 23, 24, 26, 28, 31, 32, 36, 37, 38, 40, 44, 45
	Lack of government support	"There was not much support for the rehabilitation department. The focus shifted from enhancing rehabilitation services to preventing COVID-19 - related deaths." [23]	16, 17, 23
	Limiting providers' income	"During the period when we were involved in the Corona virus and the number of patients decreased, we reduced the working hours of the personnel and introduced shift personnel, which naturally led to lower salaries and better financial management" [07]	07, 09, 21, 25, 27, 31, 35, 42, 43
Payment	Delayed payment mechanism	"Among the other challenges of this era was the late payment of salaries and overtime, which had a negative impact on the therapist from a mental point of view, and the therapist's worries increased." [41]	33, 41
	Inadequate salary	"Medical personnel should receive better treatment during such crises, but we performed poorly in this area and, despite warning the policy-makers, the remuneration of the medical staff was low." [19]	19
	Unwillingness to pay for online services	"There was also a problem with paying for online services because patients thought that the therapist should work with them physically." [40]	35, 36, 40
Behavior	Mental pressures	"The patients were under stress, and the majority of them had COVID-19 infections, depression, low motivation, and feelings of hopelessness." [31] "Emotional and psychological challenges were the constant worry about disease transmission." [34] "Both therapists and families are under stress and mental pressure, especially if they visit the elderly." [44]	02, 03, 04, 08, 09, 15, 16, 17, 18, 19, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 33, 34, 37, 39, 40, 41, 42, 44, 45
	Unknown nature of COVID-19	"One of the challenges was the unknown nature of the virus, and the other was the unknown side effects of the disease and the side effects of the drugs the patients were taking." [20]	16, 20
	Fear of contracting COVID-19	"The fear of getting COVID-19, the fear of being hospitalized and the consequences after COVID-19, this stress that was inflicted on us made it much more difficult for us." [28] "The first thing that was very bad and became a challenge was the sharp decrease in the number of people visiting the clinic due to the fear of getting infected with COVID-19." [42]	01, 02, 03, 04, 06, 07, 08, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 23, 24, 26, 28, 32, 36, 38, 42, 45
	Delayed referral	"During the COVID-19 era, there were fewer clients and people were postponing their need for orthotics and prosthetics services." [03]	02, 03, 04, 05, 38
	Lack of effective follow-up	"The patients were very resistant to rehabilitation and because they did not see any progress, they canceled the treatment." [38] "Many families stopped the rehabilitation treatment and then the child severely regressed." [39]	19, 32, 36, 38, 39, 43
	Resistance to the use of online routes	"Colleagues, especially old ones, were very resistant to online services. For example, old therapists who have older approaches believed that online services lower the value of the field, and families resisted because they could not do the interventions at home, which made them abandon online services." [39] "Patients are resistant to new methods or new rehabilitation approaches such as online services." [41]	05, 10, 19, 24, 31, 34, 36, 37, 39, 40, 41, 43, 44
	Fatigue among practitioners	"In the discussion of physical occupational therapy, the increase in heat led to the therapist's fatigue and I had breathing problems." [35] "Working with coverings like masks was extremely terrifying. The effects of the mask are still on their faces and the redness has not disappeared." [45]	31, 32, 35, 39, 40, 41, 42, 43, 45
	Unwillingness to service delivery	"Patients who were at home and needed oxygen after contracting Corona, needed a home visit. Many colleagues resisted not to do this because they knew they were COVID-19 patients." [17]	17, 40, 42

Tab. III *(follows).* Identified challenges in delivering physical rehabilitation services during the COVID-19 pandemic in Iran.

Main themes	Challenges	Direct quotes	Participants' ID
Behavior	Isolation of practitioners	"Due to the fact that some members of the public thought that the health workers might be infected with COVID-19, they refused to communicate with this group."	28
	Reducing the motivation	"Sometimes the therapist had low motivation, which lowers the quality of service." [45]	36, 45
	Absenteeism	"The absence of patients or the absence of the therapist due to the infection of COVID-19 caused the process of providing services to be disrupted." [33]	33
	Lack of effective teamwork	"I feel that unfortunately there is no good communication between nurses and physiotherapists in Iran. It means that it is not a good teamwork." [29]	29
	Annoying of protective equipment	"Because of the mask on our face, the oxygen was very low. I had headaches and dizziness every night." [25] "The therapist could not provide sufficient explanations with protective covers such as a mask, or the clients who used the mask could not perform the exercises properly due to breathing problems." [34]	03, 10, 17, 18, 20, 22, 23, 25, 28, 32, 34, 38
	Disruption of communication	"I think connecting with patients was our biggest challenge, and even though we followed the protocols very sensitively, we were still worried about that." [13] "In mental occupational therapy, exercises such as smiling or facial feedback were influenced by the mask." [35]	03, 04, 13, 34, 35, 36, 39, 42, 43, 45
	Superstitions	"In the area where I was in Zahedan, there was a lot of discussion of medical superstitions, religious beliefs, especially among fellow Sunni citizens, and going to the doctor happened later." [30]	30
	Decreasing the family supports	"The physical presence of the families supporting the elderly had also decreased, for example, they had reduced their visits to their grandparents' house, exercises were not done at home. And the improvement process of people who referred to occupational therapy was very weak." [44]	32, 44
	Failure to comply with health protocols	"One of the biggest challenges was that some people did not follow the protocols, that is, they did not use masks correctly and did not take the disease seriously." [02]	02, 03, 06, 12, 44
	Limitation of patients' movement maneuvers	"During the COVID-19 era, patients were limited in exercise because they were dependent on oxygen." [41]	41
	Cultural challenges	"Another problem was the lack of cooperation of the families who did not want to make phone or video calls." [38]	35, 38
	Lack of trust in telerehabilitation	"Families did not trust remote rehabilitation and did not look at it as a treatment method, and it was hard to convince them about this treatment method." [35]	35
	Unawareness among users	"Awareness about occupational therapy is low in the society and it was even worse during the corona virus." [38]	25, 27, 33, 35, 38, 40
	Lack of familiarity in working with online platforms	"Patients, especially the elderly, did not know how to use some platforms, they had phones but did not know how to use applications." [31] "Patients were not updated, did not know how to use different programs and did not have enough access to different programs." [34]	31, 33, 34, 40
	Lack of familiarity with modern rehabilitation services	"Because we were not prepared for these conditions beforehand, we were not familiar with the new rehabilitation services." [33]	33, 42

Solutions

In response to the various challenges posed by the COVID-19 pandemic, PR facilities had to adopt appropriate strategies to implement diverse solutions for overcoming the challenges. The interviewees proposed solutions spanning various domains, including the immediate healthcare landscape and broader socioeconomic and policy considerations. These solutions, categorized according to the five control knobs, can offer a comprehensive framework for addressing the complex challenges identified.

The study participants highlighted the importance of strengthening telerehabilitation and moving towards online services at the organizational level. During the lockdown, telerehabilitation could help to maintain PR services while reducing the risk of disease transmission. Services provided through telerehabilitation range from education and consultation to assessment and therapy. Despite the limitations of telerehabilitation, studies have demonstrated that in certain conditions, its effectiveness may match that of in-person PR [45]. We also highlighted the importance of improving internet connectivity to support online services and developing practical

Tab. IV. Identified solutions in delivering physical rehabilitation services during the COVID period in Iran.

Main themes	Sub-themes	Direct quotes	Participants' ID
Organization	Strengthening the macroeconomics	"For example, the Philippines was able to be locked down for a long time because it had a good economy and killed a very small number of people. Therefore, it is necessary that the economic situation of the society should be such that it can provide social distancing and good financial support during such conditions." [18]	18
	Creating a resilient health system	"At the national level, an agile health system should be created that can quickly act in prevention, treatment and rehabilitation during crises." [25]	01, 19, 25, 34
	Involving of rehabilitation experts in policy-making	"Rehabilitation specialists should have a greater role in the process of formulating health policies. Unfortunately, in Iran, because there are more doctors and nurses, their influence on policies is more impressive." [30]	30
	Considering rehabilitation services in policies	"Although the hospital guard was paid a bonus for the period of COVID-19, we physiotherapists were not paid anything. Therefore, it is necessary that rehabilitation professionals are also considered in incentive policies according to the nature of their work." [22]	22
	The possibility of direct access to practitioners	"In my opinion, it should be possible for the physiotherapist to visit the patient directly." [29]	29
	Facilitating the public transportation	"It is very important to pay attention to the transportation of patients. Responsible institutions should facilitate this." [02]	02, 16
	Facilitating home-based care	"Service delivery methods such as home-based services should be considered more during such crises as they greatly reduce the risk of contracting the disease." [05]	02, 05, 08
	Using charities and NGOs	"The capacity of charities and non-governmental organizations can be used to provide rehabilitation services, especially for disadvantaged and vulnerable groups." [20]	20
	Using private sector capacity	"Most of the rehabilitation services in Iran are provided by the private sector. It is necessary to use the capacity of this department especially in crises." [06]	06
	Establishing a comprehensive information system	"Access to a comprehensive system is necessary to provide useful information to families and therapists." [40]	40
	Timely vaccination	"As I mentioned, simultaneous and timely vaccination of both therapists and clients could lead to the improvement of service delivery." [02]	02, 04, 06, 07, 18, 35
	Effective crisis management	"We did not have a clear crisis management during this pandemic. In the long COVID-19 period, it is necessary to pay more attention to crisis management with a focus on prevention." [31]	17, 31, 34
	Facilitating the integration of services in inpatient department	"A group of therapists started to set up occupational therapy department in inpatient wards. The flourishing period of occupational therapy was at that time because for the first time occupational therapy for inpatients was introduced into the hospital service system and it was the first time that occupational therapy services were provided in inpatient departments." [31]	30, 31
	Careful informing	"Organizations such as the Ministry of Health should provide the necessary training and provide detailed information." [06]	02, 06
	Using social media	"Social media should justify people correctly and give people correct information because we used to get most of the information from social media." [39]	19, 25, 39
	Improving the internet	"My proposal for the government is to improve the Internet. For example, our online classes were closed due to the internet outage and the patients suffered a lot." [16]	16, 36, 44
	Appropriate clinical environment	"A suitable space with proper ventilation can lead to better rehabilitation services." [32]	13, 14, 27, 32, 38, 42
	Applying modern devices and instruments	"I think the use of equipment such as scanners, which leads to a reduction in direct contact with patients, can be effective." [10]	10, 45
	Structured waiting list	"It is better to adjust the attendance schedule of patients in such a way that there is no interference and crowding in the clinic environment." [14]	14
	Moving towards online services	"One of the good things that COVID-19 led to was that we went towards to online rehabilitation." [32]	08, 12, 32, 36, 37, 43
	Creating practical applications	"A suitable solution is to prepare and set up appropriate computer games, such as applications that perform exercises step by step and enter the next step." [38]	36, 38, 43

Tab. IV *(follows).* Identified solutions in delivering physical rehabilitation services during the COVID period in Iran.

Main themes	Sub-themes	Direct quotes	Participants' ID
Organization	Strengthening the telerehabilitation	"There is a need to strengthen telerehabilitation services in Iran so that services can be provided during pandemics such as COVID-19." [16] "Telerehabilitation made people in some cities who did not have access to have access to therapists, even at that time patients from southern cities visited and the patients made progress." [39]	01, 05, 16, 19, 22, 31, 33, 34, 35, 36, 38, 39, 42
	Mobile rehabilitation team	"Mobile rehabilitation teams can be used to provide services, especially to deprived and remote areas during pandemics." [40]	40
	In-service training	"The training should be done by universities or centers that have the authority to teach, and the therapists should be taught what they can do in this course, for example, explain infection control strategies or other issues." [35]	31, 35, 39
	Holding online courses	"Holding workshops online became more intense and I think it was one of the turning points of that period." [21]	21, 26, 28
	Providing distance education	"There is a need to provide platforms, especially in the field of education, for example, to adapt to educational systems and virtual education." [01]	01, 33
	Adjusting the educational curriculum	"There is a need to pay more attention to issues related to infectious diseases in the curriculum of rehabilitation courses." [25]	25
	Preparing high quality evidence	"Also, conducting high-quality research and studies in the field of rehabilitation and using their results in the post-COVID era can lead to very good results." [01]	01, 27
	Free services for vulnerable groups	"People who were economically low were not charged, the treatment was free for them." [33]	32, 33
	Enhancing the accessibility to PPE	"The provision of personal protective equipment such as masks and gloves, as well as vaccination, led to the improvement of service delivery during this period." [04]	04, 24, 27, 45
	Pay more attention to health workforce	"Policies should be adopted to pay more attention to the personnel of special care departments such as nurses, infectious disease specialists, anesthesiologists and therapists." [19]	19
Regulation	Establishing effective clinical guidelines	"Professionals should come up with a protocol for how to provide services in the new pandemic." [18] "It is necessary to standardize the terms of service provision." [19]	18, 19, 35, 40
	Defining tariffs for online services	'Tariffs for online services should be clearly defined in order to create a sufficient incentive for providers." [35]	35
	Realizing the tariffs for rehabilitation services	"Tariff rates are not realistic for many rehabilitation services. Due to the high rate of inflation, it is necessary to review them." [19]	19
Financing	Improving the insurance coverage of rehabilitation services	"There is a need to improve the insurance coverage of rehabilitation services to reduce the co-payment of recipients." [11]	11
	Insurance coverage for online services	"Health insurances should also cover online services." [39]	39
	Increasing the government supports	"Government support should be increased. For example, taxes should be removed during the pandemic period, or incentive points should be considered for therapists who accepted the risk of providing services during this period." [09]	09, 33, 42, 44
Payment	Reducing out-of-pocket	"A major part of the cost of rehabilitation services is paid OOP. Therefore, solutions should be made to reduce this cost." [24]	24
	On-time payment by insurers	"One of the constant challenges of Iranian health insurance is late reimbursement. Therefore, to improve the motivation of clinicians, it is necessary that reimbursements be made on time." [27]	27
	Considering rehabilitation providers in the payment of bonus	"Rehabilitation professions are often overlooked when it comes to rewarding hard work during crisis situations." [31]	31

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applications to reduce the need for in-person interventions. We noted that timely vaccination, a suitable clinical environment, and improved accessibility to PPE serve as solutions for controlling disease transmission during in-person visits. Our participants' recommendations align with the growing body of research highlighting

Tab. IV *(follows).* Identified solutions in delivering physical rehabilitation services during the COVID period in Iran.

Main themes	Sub-themes	Direct quotes	Participants' ID
Behavior	Increasing the awareness of physicians	"It is very important to increase the awareness of doctors about rehabilitation services, especially the services needed in acute stages." [31]	07, 31, 37, 39
	Increasing public awareness about telecommunications	"The most important solution is that you should familiarize the whole community with remote communication devices in advance, such as smart watches that are really therapeutic and can be connected to the therapist's system and the therapist can check a number of things remotely or how to use many Teach the cases." [31]	31, 35, 40
	Improving the public awareness regarding pandemic	"There is a need to raise public awareness of both pandemics and rehabilitation services." [36]	36, 38
	Effective teamwork	"In times of crisis, one of the things that is very important is to work as a team where the whole hospital has the duty to fight for a goal." [41]	06, 22, 26, 41
	Improving provider-user relationship	"Many times, the patients could not communicate with us properly because of the psychological problems caused by the corona virus. So this requires a close relationship between us and them." [23]	02, 23
	Adherence to safety protocols	"I think that cleaning the service delivery environment in order to lower the risk of infection for therapists and even patients can be very effective." [08] "I think it is possible to provide safer rehabilitation services only by following health protocols." [13]	08, 13, 15, 16, 32, 39
	Promoting responsibility	"The more important factor was that some people really need help and they cannot be abandoned from a human and moral point of view." [18]	18, 25, 28, 36
	Use of medical aids	"It is necessary for the general public to be familiar with medical aids such as pulse oximetry, biofeedback, etc." [31]	31
	Strengthening spiritual dimensions	"Let's not look at the financial aspect 100% in our work and consider the spiritual side somewhere." [31]	31
	Psychological support	"My advice is that we should take a series of psychological courses, not in a completely professional way, but in such a way that we can adjust our intimacy and behavior with the patient so that he can reduce his mental challenges and trust us more easily." [23]	23, 41
	Increasing the flexibility	"I learned flexibility and patience during this pandemic. I learned to be patient and interact with the patient better." [16]	16
	Delivering evidence-informed interventions	"To treat the patients, at first, drugs were used that were not based on evidence and a lot of money was spent on it, which shows that just having wealth without knowledge does not help the country. Therefore, there is a need to provide interventions based on reliable scientific evidence." [19]	19, 22
	Having holistic view	"My recommendation is to hold a psychological webinar and teach how to deal with the patient. Some patients said that the therapists only put the device on our body, without saying a word or anything." [23]	23, 28

the need for intersectoral collaboration, technological advancements, and policy reforms to enhance the resilience and adaptability of healthcare systems in the face of crises [46, 47]. The participants stressed the necessity of developing clinical guidelines for PR services during the COVID-19 pandemic. By standardizing service provision and creating protocols tailored to the new pandemic environment, healthcare systems can enhance their ability to respond effectively to emerging challenges and ensure the quality of care provided to patients. Defining clear and fair tariffs for PR services, including those provided online, not only ensures transparency, but also promotes the adoption of online PR solutions, ultimately enhancing patients' access to care.

The participants proposed increasing the government's financial support and reducing OOP payments for PR services as solutions to bolster the healthcare system and make PR services more accessible and equitable for all. Different strategies for reducing OOP payments in the health system and expanding financial support in PR have been studied [48]. Adopting proper strategies is necessary for progress towards universal health coverage.

Increasing the awareness of physicians and the public regarding PR services was pointed out by the participants. The emphasis on empowering healthcare workers, providing psychological support, and fostering effective teamwork and communication aligns with the growing recognition of the importance of addressing the well-being and professional needs of the healthcare workforce, particularly during challenging times [49-51]. By prioritizing the needs of both providers and patients, healthcare systems can create an environment conducive to the delivery of high-quality, sustainable PR services [52].

Limitations

Like all other studies, our study also had some limitations. In the following, we will mention some of these limitations. Firstly, the study might not have fully included the experiences of those in rural areas or different types of facilities if the majority of participants were from cities or certain hospitals. Secondly, the findings may not apply to other places outside Iran because each has its own culture, healthcare setup, and government rules that could be very different. Thirdly, personal opinions and viewpoints may have influenced the collection and interpretation of the data. This might have affected how reliable and accurate the findings are.

Conclusion

The main identified challenges included Iran's healthcare system's lack of preparedness, deficient infrastructure, limited remote PR options, restriction of in-person visits, lack of comprehensive clinical guidelines, ambiguous pricing for telerehabilitation, financial hardships stemming from the pandemic, insufficient government support, reliance on OOP, patients' reluctance to pay for online services, delayed compensation for PR professionals, mental distress experienced by patients and service providers, resistance to new service modalities, and inadequate digital literacy. In response to these multifaceted challenges, the study participants proposed a range of solutions. The key solutions included strengthening telerehabilitation infrastructure, developing clear clinical guidelines, increasing government financial support, improving payment structures, and fostering behavioural changes through increased awareness.

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Ethics approval and consent to participate

The Research Ethics Committee of the Shiraz University of Medical Sciences provided ethical approval for this study (IR.SUMS.REC.1402.399) previously. All methods were performed in accordance with the relevant guidelines and regulations such as Declarations of Helsinki. Informed consent for participating in this study was obtained from all the participants before the interview sessions.

Consent for publication

Not applicable.

Availability of data and materials

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

Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contributions

P.M, P.Mo, N.E, S.SH, M.B, and AH.KN contributed to the conception and design of the study. P.M, T.A, N.E, A.T, and AH.KN conducted the interviews, and S.SH, P.Mo, and M.B were co-moderators. P.M, T.A, A.T, AH.KN, and S.SH conducted most of the analysis, which P.M and M.B discussed regularly. P.M, P.Mo, N.E, S.SH, M.B, AH.KN, MM performed a search of the literature. P.M, P.Mo, M.B. and S.SH wrote the initial draft, and T.A, N.E, A.T and MM contributed to manuscript revisions. MB and MM: editing. All authors read and confirmed the final manuscript.

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Infectious Diseases

Zika Virus Disease in India

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Keywords

Zika virus disease

In 2024, a total of 151 Zika virus disease (ZVD) cases were reported in India (from Maharashtra, Karnataka, and Gujarat States). Maharashtra reported 140 cases (125 cases from Pune), Karnataka 10 cases (7 cases from Bengaluru) and Gujarat 1 case (1 case from Gandhinagar) respectively. No case of microcephaly or Guillain-Barre syndrome (GBS) associated with this outbreak was reported [1].

India reported its first Zika case from Gujarat State in 2016. Since then, many other States namely Tamil Nadu, Madhya Pradesh, Rajasthan, Kerala, Maharashtra, Uttar Pradesh, Delhi, and Karnataka have reported cases subsequently, but no ZIKV-associated microcephaly has been reported. Aedes mosquito density in India varies by season and location, with the highest densities occurring during the monsoon and post-monsoon seasons [1].

The Zika virus disease is usually mild and requires no specific treatment. The most common symptoms are mild fever, skin rash, headache, muscle and joint pain and inflammation of the underside of the eyelid. These symptoms normally last for 2-7 days [2].

In India, Zika outbreak occurred in 2017 and in July 2021 one laboratory-confirmed case was also reported in Kerala state. One study was conducted to assess any positivity in field-collected mosquitoes for ZIKV and DENV during 2016-2021. Mosquito samples were received from 4 Zika affected citites, whereas samples were collected from Delhi. Out of 2346 pools, 4 pools for ZIKV, and 23 pools for DENV were found positive. ZIKV positive pools were from Jaipur (3 pools) and Kanpur (1 pool). 10 localities of Delhi were found positive for DENV. It was observed that the maximum positivity rate for both viruses were found in September-October [3].

Another study showed that the lower attack rate of ZIKV in children than in adults will hasten the emergence of a population that will be fully susceptible to infection. Even with lifelong immunity, children aged 0-14 years will become entirely susceptible by 2031 and 15-29 year olds by 2046. In future outbreaks, the attack rate will then be highest amongst 15-29 year olds, including women who will be at risk of ZIKV infection in pregnancy [4].

With the limited data available, it is seen that ZVD cases are rising and vary regionally across different states. The difference can be due to variation in number of tests done in all regions (state and city) due to different reasons. Hence, samples should be homogenously taken from different region including from hard to reach areas for understanding better picture. The case load appears to be underreported because asymptomatic infection and unreported illness are generally not taken into consideration, overlapping symptomatology of ZVD with dengue and chikungunya, and different level of health care providers' awareness about the disease. Rising number of ZVD in India and future possibility of increased susceptibility among children and young adults mandates continuous monitoring, surveillance and use of preventive measures.

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Conflict of interest statement

None.

Authors' contributions

DS made substantial contributions to conceptualization, investigation, writing-original draft, and writing-review & editing.

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Infectious Disease

Hepatitis C Virus Infection in Hemodialysis in Cameroon: Prevalence and Incidence

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Keywords

Hepatitis C Virus • Hemodialysis • Prevalence • Incidence rate • HCV-RNA

Summary

Background. *Hemodialysis (HD) is the world's most prevalent kidney replacement therapy for end-stage renal disease patients. Hepatitis C virus infection (HCV) is highly prevalent in patients undergoing HD. There are no reports of the epidemiology of HCV viremia and HCV incidence rate based on prospective studies in HD units in Cameroon. This study evaluated the prevalence and incidence rate of HCV based on anti-HCV antibody (Ab) and HCV-RNA detection.*

Methods. *We conducted a controlled prospective study in three hemodialysis centers in Cameroon, from October 2021 to January 2023. The HEXAGON HCV rapid kit was used to detect anti-HCV Ab, and HCV-RNA was searched using the Xpert® HCV Viral Load technology. We performed a Wilcoxon test and the chi-square or Fisher exact test in statistical analyses.*

Results. *A total of 205 HD patients were enrolled with a mean age of 47.7 ± 14.5 years and median hemodialysis duration of 36 months (IQR: 12-72). Anti-HCV Ab was positive in 59 patients, giving a prevalence of 28.8% (95% CI: 22.7-35.5). This Anti-HCV Ab infection was mainly found in patients with a relatively long period of HD (P = 0,00002). Of the 59 anti-HCV Ab-positive patients, HCV-RNA was detected in 42, with the HCV active infection prevalence of 71.2% (95% CI: 57.9-82.2). A high viral load (HCV RNA > 800,000 UL/ml) was detected in 31% (95% CI: 17.6-47.1). A total of 125 patients with a negative status at the start of the study (M0) were prospectively followed up. After seven months (M7), 15 [12%; 95% CI: 06.9-19.)] became HCV positive, with an incidence rate of 20.6 cases per 100 patients-years.*

Conclusion. *There is a high prevalence of HCV infection and HCV incidence rate in this study. Strategies aimed at decreasing HCV infection in HD centers in Cameroon are urgently needed.*

Introduction

Hepatitis C virus (HCV) is a ribonucleic acid (RNA) virus belonging to the family *Flaviviridae;* that is responsible for hepatitis C liver disease. He may be responsible for mild inflammation (acute hepatitis) or severe and persistent inflammation (chronic hepatitis) of the Liver. It is estimated that 50 million people have chronic HCV infection, and 1.0 million new infections occur each year [1]. Hemodialysis (HD) is the most prevalent kidney replacement therapy for patients with end-stage renal disease (ESRD) globally, accounting for approximately 69% of all kidney replacement therapy and 89% of all dialysis [2-4]accessibility, quality, and affordability**.** People undergoing HD are known to be at high risk of HCV infection [5HCV and HIV infections in patients with hemodialysis. Patients and methods: A retrospective study of 430 end-stage renal failure patients, referred to hemodialysis department at XXXX Teaching Hospital, Baghdad-Iraq from January-2015 to January-2017. Patients were investigated for HBs-Ag using enzyme-labeled antigen test (Foresight-EIA-USA-8]. Indeed, this high susceptibility of HD patients to acquire HCV infection is due to their frequent hospital admissions and the high frequency of invasive procedures [6]. The prevalence of HCV infection in HD units varies greatly across geographical regions and over time [9]. At the global level, this prevalence is estimated at 24.3%, with the highest observed in lower-middle-income economies (26.8%) [10]. Regarding the incidence rate of HCV infection, the Dialysis Outcomes and Practice Patterns Study (DOPPS) phase 1 study showed a decrease in the incidence of HCV from 2.9 to 1.2 per 100 patient-years in HD units in the United States, Europe, and Japan [11]. In contrast, this incidence remains high (4.44 per 100 patient-years) in the developing world [12]. As the number of patients with chronic kidney diseases requiring hemodialysis as a renal replacement therapy is growing, HCV infection and transmission are increasingly frequent and need to be emphasized in worldwide hemodialysis units. In Cameroon, only two studies have reported HCV prevalence in HD patients: the first at 19,2% in Buea and Bamenda HD centers (South West region and North West region) and the second at 26.3% in Yaounde University Teaching Hospital (Centre region) [13, 14]. However, these prevalences were only based on the antibody assay, which cannot differentiate HCV infection (anti-HCV antibody positive) from active HCV infection (viral RNA detection)

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which is reflective of replication and infectivity of the virus. Moreover, the burden of HCV remains unknown in HD centers in the South (Ebolwa), East (Bertoua), and North (Garoua) regions of Cameroon. In the setting where many reports have suggested a nosocomial patient-to-patient mode of transmission of HCV in HD units, HCV viremic patients could be the source of this transmission. A direct test for HCV viremia is thus necessary to identify infectious subjects in HD units. Some retrospective studies reported that the rate of HCV seroconversion in HD patients in Cameroon is between 7.1% and 25%, and only one study reported the HCV incidence rate at 3.6 per 100 patient-years [15Biorad-17]. In comparison to prospective studies, retrospective studies cannot demonstrate the real incidence rate because they are prone to different biases, particularly recall bias.

This study was conducted to determine the prevalence of anti-HCV antibody, active HCV infection, and HCV incidence rate in three hemodialysis centers in Cameroon, to stimulate health policies to implement strict infection control measures in Cameroonian hemodialysis units.

Methods

Study Design, Sites, and Population

This was a controlled prospective study conducted from October 17, 2021, to January 21, 2023, in three hemodialysis centers in three regions of Cameroon: The Ebolowa Regional Hospital Hemodialysis Centre (ERHHD, South Cameroon); Bertoua Regional Hospital Hemodialysis Centre (BRHHD, East Cameroon); and the Yaoundé General Hospital Hemodialysis Service (YGHHD, Centre Cameroon). The study was carried out over seven months in each center, and the samples were taken in two rounds: in month 0 (M0) and later in month 7 (M7). The study was carried out in the Cameroon hemodialysis patients' community. The included patients met the following criteria: 1) aged over 12 years irrespective of sex and ethnicity; 2) undergoing hemodialysis for end-stage chronic kidney disease (ESCKD-stage 5 GFR < 15 ml/min/1.73 m); 3) had been on hemodialysis for a minimum duration of 3 months; and 4) provided signed informed consent or parental assent. Demographic data (including age, gender, study level, marital status, and occupation) and hemodialysis data (including vascular access, HD duration, blood transfusion history, dialysis groups, and attending several dialysis centers) were obtained by direct interview of patients and completed by review of their medical records.

Sampling and hepatitis C virus assays

A volume of 5 mL of blood was collected either before the stated hemodialysis session (during patient connection); or thirty minutes before the end of the hemodialysis session, to avoid PCR inhibition by heparin. The blood was collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and then centrifuged at 2500 rpm for 10 minutes. Thereafter, 1.5 mL of plasma was collected in Eppendorf tubes and then placed in an icebox (containing ice packs) for transportation to the Centre Pasteur of Cameroon (CPC), where all analyses were performed. At the CPC, the plasma was subsequently stored at -80°C. The HEXAGON HCV for rapid and qualitative detection of IgG antibodies to HCV in human serum, plasma, or whole blood with a sensitivity of 99.3% and a specificity of 99.5% was used. It is an immunochromatographic assay using recombinant antigens from structural (Core) and nonstructural (NS3, NS4, and NS5) regions of the HCV genome, known to be highly immunodominant. Briefly, 10 µl of plasma was applied onto the sample port (S) of the "TEST" device, and three drops of "DIL" solvent were added. The results were read within 5-20 minutes at a well-lit place. The detection and quantification of HCV-RNA were performed in all patients who tested positive for anti-HCV Ab. We used GeneXper Dx Systems, which uses the Xpert® HCV Viral Load (Cepheid Röntgenvägen 5, SE-171 54 Solna, Swede) technology with an assay sensitivity of 10 copies/mL. The Xpert® HCV Viral Load is an automated test, whose cartridge integrates HCV-RNA extraction, amplification, and detection of the target sequences (5' untranslated transcribed region) using real-time reverse transcriptase polymerase chain reaction (RT-PCR). Briefly, slightly more than 1 mL of plasma was introduced into the sample chamber of the test cartridge using the transfer pipette included in the kit. The lid was then closed, and the cartridge was loaded into the GeneXpert Dx instrument.

Clinical data and definitions

Active HCV infection (virus infectivity) was defined by the presence of viral RNA in the plasma. High viral load was defined by HCV RNA > 800,000 UL/ml [18]. Newly HCV-infected patients: patients who were seronegative for anti-HCV Ab at the beginning of the study (M0), and became anti-HCV Ab positive at the end of 7 months.

Ethics Statement and Statistical Analyses

Our research protocol was approved by the Comité National d'Ethique de la Recherche pour la Santé Humaine (CNERSH), N° 2021/07/91/CE/CNERSH/SP. The statistical analyses were performed using RStudio version 4.1.0 software. The Kolmogorov-Smirnov test allowed us to verify the normality of our quantitative variables that were expressed as the mean ± standard deviation or as the median interquartile range ((IQR): 1st-3rd) according to the normal distribution or not. Chi-square or Fisher exact tests were used to compare the proportions as applicable, and Wilcoxon tests were used to compare qualitative and quantitative variables. *P* values less than 0.05 were considered statistically significant.

Results

Demographic and hemodialysis data

A total of 205 HD patients (169 from YGHHD, 24 from ERHHD, and 12 from BRHHD) including 85 (41.5%)

Tab. I. Distribution of HCV positivity according to demographic and hemodialysis data.

Anti-HCV Ab Positive (N=59)						HCV-RNA Positive (N = 42)				
Data	Variables		a	b (95%IC)	P value	Variables		a	b (95%IC)	P value
Socio-demographic data	HD Centres	ERHHD (n=24)	14	58.3 (36.6-77.9)	**0.003***	HD Centres	ERHHD (n = 14)	10	71.4 (95%CI :41.9-91.6)	0.14
		YGHHD (n=169)	43	25.4 (19.1-32.7)			YGHHD (n = 43)	32	74.4 (95%CI :58.8-86.5)	
		BRHHD (n=12)	2	16.6 (2.1-48.4)			BRHHD (n = 2)	0	0 0 (95%CI :0-84.2)	
	Sex	M	37	62.7 (49.1-75)	0.44	Sex	M	25	59.5 (43.2-74.4)	0.61
		F	22	37.3 (25.1-50.9)			F	17	40.5 (25.6-56.7)	
	Age group	11-21	1	1.7 (0.0-9.1)	0.11					
		21-31	5	8.5 (2.8-18.7)						
		31-41	11	18.6 (9.7-30.9)						
		41-51	10	16.9 (8.4-29)						
		51-61	15	25.4 (15-38.4)						
		61-71	13	22 (12.3-34.7)						
		71-81	4	6.8 (1.9-16.6)						
		81-91	0	0 (0-6.1)						
HD Data	HCV Initial status	Positive	13	22 (12.3-34.7)	NA					
		Negative	17	28.8 (17.7-42.1)						
		Unknown	29	49.2 (35.9-62.5)						
	Blood transfusion	No	9	15.2 (7.2-27)	0.52					
		< 5	15	25.4 (15-38.4)						
		> 5	35	59.3 (45.7-71.9)						
	Vascular access	Catheter	9	15.2 (7.2-27)	0.77					
		Fistula	50	84.7 (73-92.7)						

a: Frequency; b: Percentage; BRHHD: Bertoua Regional Hospital Hemodialysis Centre; ERHHD: Ebolowa Regional Hospital Hemodialysis Centre; YGHHD: Yaounde General Hospital Hemodialysis Service; HD: Hemodialysis; NA: Not Applicable, *: Statistically significant.

females and 120 (58.5%) males, were included in this study. The mean age of the participants was 47.7±14.5 years (range: 12-86), and the hemodialysis duration ranged from 3 to 324 months with a median of 36 months (IQR: 12-72).

Prevalence of anti-HCV antibody and active HCV infection

Of the 205 included participants, 59 tested anti-HCV Ab positive, with a prevalence of 28.8% (95% CI: 22.7-35.5). This prevalence was significantly different between HD centers: 58.3% (95% CI: 36.6-77.9) at ERHHD, 25.4% (95% CI: 19.1-32.7) at YGHHD, and 16.6% (95% CI: 2.1-48.4) at BRHHD (P=0.003). The majority of anti-HCV Ab-positive patients were men [62.7% (95% CI: 49.1-75)], and the age range was 51-61 years [25.4% (95% CI: 15-38.4)] (table I). By comparing the median duration of HD between anti-HCV Ab positive patients [60 (IQR:36-84) months] and anti-HCV Ab negative patients [24 (IQR:12-60) months], we found that HCV infection mainly affected patients with a relatively long period of HD (P = 0,00002). Of the 59 anti-HCV Ab-positive patients, HCV-RNA was detected in 42, giving a prevalence of HCV active infection at 71.2% (95% CI: 57.9-82.2). This prevalence of HCV infectivity was very similar in ERHHD [71.4% (95% CI: 41.9-91.6)] and in YGHHD [74.4% (95% CI: 58.8-86.5)]. The median HCV RNA viral load was 207,000 IU/mL (IQR: 7,135- 863,322), and 31% (95% CI: 17.6-47.1) had a high viral load.

HCV incidence rate

At the start of this study (M0), 44 patients (21.5%; 95% CI: 16-27.7) were anti-HCV Ab positive, and 161 (78.5%; 95% CI: 72.3-84) were anti-HCV Ab negative. Among these 161 negative M0 patients, 125 were successfully followed up for a total duration of seven months (M7). Indeed, 36 patients were lost to follow-up for several reasons: death, impaired health leading to rejection of serological testing repeat, and transfer to another HD centers. At the end of the follow-up (M7), 15/125 [12%; 95% CI: 06.9-19.)] patients were confirmed to be newly HCV infected, for a total incidence rate of 20.6 cases per 100 patient-years (p-y). This incidence rate was 34.3 cases per 100 p-y in ERHHD [2/10 (20%; 95% CI: 02.5-55.6)], 21.1 cases

per 100 p-y in YGHHD [13/106 (12.3%; 95% CI: 06.7-20.1)], and 00.0 cases per 100 p-y [00/9 (00%; 95% CI: 0-33.6)] in BRHHD (P = 0.0398). Of the 15 newly HCV-infected patients, only one had undetectable levels of HCV RNA, and two had a high viral load (14,3%; 95% CI: 1.7-42.8).

Discussion

Currently, it is well known that HCV is the main viral infection found in patients undergoing HD. The burden of HCV infection among HD patients has been widely documented, but it is different across countries and between HD units in the same country. This study is the first to determine the prevalence of active HCV infection, and the HCV incidence rate among maintenance hemodialysis patients in Cameroon based on a prospective study.

The prevalence of anti-HCV antibody found in this study (28.8%) is slightly higher than those obtained by Luma *et al* in 2017 and Ndomgue *et al* in 2018 (19.2% and 26.3% respectively) [13, 14]. These results show that anti-HCV antibody prevalence among HD patients in Cameroon has been on the rise over the past six years. This can be explained by the fact that: because of the increasing rates of high blood pressure and diabetes mellitus in the population, the prevalence of end-stage renal disease is growing, which increases in the number of patients admitted for hemodialysis [19, 20] when the initiation of renal replacement therapy (RRT). Our prevalence is five times higher than those in the general population, blood donors, and sickle cell patients in Cameroon (6.5%; 2.5%; and 8.6% respectively) [14, 21]. Therefore, this study confirmed that patients on maintenance hemodialysis are at greater risk of acquiring HCV infection compared to the nondialyzed population. As shown in recent studies (1% in southern India, 5.4% in Iran, and 7.4% in China), the prevalence of anti-HCV antibody is low in most hemodialysis units in developed countries [22-24]. However, this study shows that this prevalence remains high in Cameroon, and this may reflect poor adherence to the standard infection control procedures recommended by the Centers for Disease Control and Prevention (CDC), and updated by the Kidney Disease: Improving Global Outcomes (KDIGO), regarding hepatitis C virus in hemodialysis units [25, 26]. Indeed, given the large population of individuals requiring hemodialysis therapy, many countries have deployed great efforts in the past few years to reduce HCV infections in this susceptible population. Implementing preventive measures to decrease HCV prevalence in HD units in Cameroon is an emergency.

We found that 71.2% (42/59) of the anti-HCV Ab-positive HD patients in this study were HCV-RNA viremic, which is consistent with studies performed by Miyasaka *et al.* (68.9%), and Albayati *et al.* (83.3%) [27, 28]. Our study confirms the assertion that most patients with anti-HCV Ab in HD units have active HCV infection. In this study, 31% (13/42) of HCV-RNA viremic patients had a high viral load (HCV RNA > 800,000 UL/ml) and could be the source of nosocomial transmission of HCV. Indeed, many studies that investigated local HCV infection outbreaks within dialysis settings found common evidence that suggests a nosocomial patient-to-patient mode of transmission [29-35]. It is therefore recommended that anti-HCV Ab-positive HD patients should undergo HCV RNA testing to confirm active HCV infection and identify and treat infectious subjects. Because, KDIGO does not recommend isolation and the use of dedicated machines for HCV-infected patients, the high percentages of active HCV infection and high viral load found in this study suggest improvement of hygienic precautions in Cameroonian HD units, especially in regions of high HCV endemicity.

A prospective follow-up of our HCV-negative HD patients allowed us to observe a total of 15 newly acquired infections, giving an incidence rate of 20.6 cases per 100 p-y. Our rate is very high compared to the 0.4-9.4 cases per 100 p-y range previously obtained in Cameroon, Lebanon, and Morocco [17, 34, 35]. This can be explained by the differences in time of follow-up and differences in initial HCV prevalence in the HD units. Determining the evolution of the HCV burden in the HD unit is crucial to implementing reduction and elimination policies. However, the best way to determine this burden is to compare the results of past and present incidence rates. Further studies should investigate the modes of spread of HCV among HD patients to propose solutions to limit the transmission of HCV in this population.

We acknowledge some limitations in this study. (1): HCV-RNA detection and quantification have been carried out only in anti-HCV Ab-positive patients, which could underestimate our prevalence of active HCV infection and incidence rate. (2): Sequencing and phylogenetic analyses were not performed in this study, so we did not search for the different HCV genotypes circulating in our HD units or establish the route of HCV spread.

Conclusions

This study reports a high prevalence of anti-HCV antibody, active HCV infection, HCV seroconversion, and incidence rate in HD patients in Cameroon. Strategies for preventing and eradicating HCV in our dialysis units are urgently needed.

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Ethics approval and consent to participate

Ethical approval (N° 2021/07/91/CE/CNERSH/SP) was obtained from the Comité National d'Ethique de la Recherche pour la Santé Humaine (CNERSH). All samples were tested anonymously and coded, only the principal investigator had access to patients' data. All hemodialysis patients enrolled in this study signed a written informed consent, after an explanation of the objective, procedure, risks, and benefits of the project.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request**.**

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Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contributions

RKM study conception, sampling, and data analysis and drafted the manuscript; MDN and RN study conception and design, supervision of data collection, laboratory experiments, and critical revision of the manuscript; MM, VSS, AKM, and GEA participated in study coordination, data collection, and manuscript revision; SWM, MZM, and SFL participated in laboratory experiments and manuscript revision. All authors read and approved the final version of the manuscript.

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NURSING

Integration of the fundamental of care framework into the clinic (the CONFORM study): A quasi-experimental pre-post implementation study protocol

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Keywords

Patient-centred care • Nursing interventions • Quality improvement • health outcomes • Evidence-based nursing

Summary

Introduction. *Fundamental care addresses the essential physical and psychosocial needs of patients and is critical for safe, high-quality nursing practice. Despite growing awareness of its value, it remains one of the most neglected areas in clinical care. The Fundamentals of Care (FoC) Framework provides a structured approach to support its delivery, yet its practical implementation remains limited and underexplored. This study aims to evaluate the effectiveness of integrating the FoC Framework into nursing practice to reduce patient length of stay in medical and surgical wards.*

Methods. *A quasi-experimental pre-post implementation study will be conducted over 15 months in one medical and two surgical wards. The FoC Framework will guide interventions targeting key needs (nutrition, elimination, mobility, and education) identified through focus groups with nurses, patients, and caregivers. Following framework introduction, a six-month phase of individualised care will be implemented. Data on interventions and outcomes will be collected daily via the Electronic Health Record, both before and after implementation. The primary outcome is length of stay; secondary outcomes include adverse events, readmissions, patient and nurse satisfaction, turnover intentions, complaints, discharge rates, needs assessments, frequency of interventions, and goal achievement. Analyses will use t-tests or Mann-Whitney tests. Multivariable regression models will be considered for adjusting for confounding factors.*

Conclusion. *This is the first protocol that will assess the implementation of the FoC Framework in clinical practice. Findings will contribute robust evidence on its potential to improve care quality, meet essential patient needs, enhance satisfaction among patients and staff, and reduce adverse outcomes.*

Introduction

The concept of fundamental care has evolved over time, developing alongside the conceptual interpretations of nursing care, bringing attention back to fundamental care and its importance and relevance to nursing practice [1]. As early as 2013, an investigation known as the Francis Report, initiated in the United Kingdom following a series of patient safety incidents, identified poor leadership and care quality, particularly regarding essential aspects such as nutrition and elimination, highlighting the need for a radical transformation of healthcare systems [2]. More recently, the International Learning Collaborative [3] defined fundamental care as "nursing actions that respect and focus on a person's fundamental needs" and developed the Fundamental of Care (FoC) Framework as a conceptual reference [4, 5]. The FoC framework outlines all aspects involved in delivering safe, effective, and high-quality fundamental care. In this context, a previous study identified the fundamental care needs, such as nutrition, elimination, personal hygiene, mobility, and dignity [6], emphasizing that basic nursing care is highly valued and recognized by patients as necessary and important. The FoC framework underlined the necessity of integrating these various fundamental needs, encompassing physical needs (*e.g.,* nutrition, mobility, elimination) and psychosocial needs (*e.g.,* respect for choices, communication, education, and information) [7], and the importance of establishing a positive and trusting relationship with both the patient and their families/caregivers to meet these needs [8].

Subsequently, basic nursing care has also been recognized by other studies as a fundamental element of care [9] and an increasing number of studies reference the FoC Framework.

An analysis conducted in 2018, involving both nurses and patients, identified three types of factors that can influence the delivery of FoC needs: individual factors of the nurse or patient, organizational factors, and interpersonal factors. This study highlighted how these three aspects must be addressed globally because both nurses and patients share a common perspective, which influences the delivery of FoC [10]. However, FoC is recognised as one of the areas of nursing care more frequently neglected [11], resulting in missed care. Several studies highlighted the global prevalence of missed care [12-14] and reported the negative outcomes related to them. Failure to ensure adequate

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quality of nursing care leads not only to discomfort and dissatisfaction but also to broader patient safety deficiencies [15].

Neglecting FoC leads to harmful and very concerning consequences, including health complications, loss of functional autonomy, damage to dignity and self-esteem, decreased quality of life and well-being, compromised safety, and even death. Therefore, it is essential to focus on the person "as a whole", to prevent nursing care from becoming merely a set of technical activities that do not address the patient's real needs [14]. While the potentially harmful consequences of inadequate nursing care and the importance of optimizing it have been particularly highlighted for the elderly population [2, 16], it is imperative to emphasize that basic care is essential for every human being and significantly impacts quality of life, well-being, and health outcomes [17]. Kitson et al.'s (2022) study has further propelled this perspective, providing a new view that recognizes a person's fundamental care needs throughout their life span, through the initial description of what is termed the Caring Life-course Theory [18].

For all these reasons, it is crucial that not only healthcare professionals but also society at large become increasingly aware of the fundamental care needs and appreciate their optimal delivery [17]. Indeed, the current challenge is to ensure that the FoC are provided optimally [10] and a recent position statement from the International Learning Collaborative highlighted the importance of an ongoing action from healthcare leaders to prioritize FoC in clinical practice [19]. Despite greater awareness of the importance of FoC in the last decade, the existing literature still considerably lacks robust evidence on the implementation the FoC framework in clinical practice. It is necessary to develop a foundational scientific base that will enable the future development of evidence-based guidelines for healthcare professionals to deliver FoC to patients [20].

Methods

Aims

The primary aim of this study is to obtain evidence on the effectiveness of implementing the "Fundamentals of Care" – FoC framework into nursing clinical practice in terms of reduction of length of patients' stay in the Medical and Surgical wards.

The secondary aim of this study is to assess the effectiveness of the implementation of the FoC framework on a series of patients', organizational and nurses' outcomes. For patient outcomes this study will assess: 1) adverse nursing-sensitive outcomes (falls, catheter-associated urinary and bloodstream infections, pressure injuries, restraints, readmissions); 2) patient needs (elimination, nutrition, mobilization, therapeutic education, intra-team communication); and 3) patients' or their family's satisfaction. For nurse outcomes this study will assess: 1) nurse satisfaction; 2) positive impact on nurse engagement; and 3) reduction in the intention to leave. For organizational outcomes this study will assess: 1) the impact on the rate of home discharges and 2) the number of readmissions to the wads participating in this study.

Design

A quasi-experimental pre-post implementation study design will be adopted for this study. Data will be collected from the Electronic Health Records (Hospital Discharge Database), the integrated electronic medical records (EMR), and two surveys. The STROBE checklist for observational studies will be followed for the reporting of this study [21].

Study setting and sample

This study will be conducted in medical and surgical wards of the Ordine Mauriziano Hospital in Turin (Italy). The Mauriziano hospital has a substantial bed capacity, accommodating a wide range of inpatient services across various medical and surgical specialties. In this study, one medical and two surgical wards will participate.

Inclusion and/or Exclusion Criteria

Patients who meet the inclusion criteria will be recruited to this study. Inclusion criteria for patients are: 1) being adult (>18 years old); 2) being admitted to one of the medical or surgical departments participating in this study; 3) being admitted and discharged during the study period (6-months pre intervention or 6-months after intervention). For nurses, the inclusion criterion is working in the study wards during the 6-month pre-intervention or during the 6-month post-intervention phase. Exclusion criteria are patients under 18 years of age and nurses that did not work in the study wards during the entire pre-intervention or post-intervention period.

Intervention

The FOC framework [3] has been applied to some areas of person's fundamental needs, identified through focus group methodology by nurses, patients, and caregivers from the wards involved in the quasi-experimental implementation study. It has been implemented over a period of 15 months in three wards: one medical and two surgical. The intervention included the following activities:

- an average of 130 hours of training (on FOC framework, organisational models, assessment tools and data collection procedures) for the entire technical group and nursing staff in the wards participating in the study;
- modification of nursing documentation tools for care planning and handover, introducing SBAR (Situation, Background, Assessment, Recommendation) tool;
- change in skill mix staffing: increase in nursing staff from a ratio of 1 nurse per 9.5 patients in the medical area and 1 nurse per 7 patients in the surgical area to an average ratio of 1 nurse per 6 patients in both medical and surgical areas and the reduction of the

percentage of nurse assistants to 40% of the nursing staff per each ward;
- improved shared spaces such as indoor and outdoor common areas for patients;
- inclusion of volunteer association personnel presence for approximately 4-6 hours per day;
- increase in care equipment (wheelchairs, screens, bedside cabinets);
- extension of visiting hours for families from 4 hours to 8 hours per day.

Study procedures

Patients admitted to the study wards will be cared for according to the FOC framework [3] during the 6-months post implementation period. Each patient's basic needs will be assessed, a dedicated care plan will be created and implementation of targeted interventions for unmet needs will be performed. Daily interventions and outcomes will be evaluated to ensure that the patient's needs are met. The areas of need being studied include nutrition, elimination, mobility, and therapeutic education. These areas have been chosen considering the results of the focus groups performed with the nurses of the included wards. All data regarding nursing interventions and outcomes will be collected through the Electronic Health Record before and after the FoC implementation.

Primary outcome

The primary outcome will be reduction of length of stay from pre- to post-intervention. Length of stay will be extracted through the Electronic Health Records (Hospital Discharge Database).

Secondary outcomes

Several secondary outcomes will be considered. Firstly, all secondary outcomes will be analysed in terms of absolute number for a direct comparison of each outcome between the pre- to post-intervention and in terms of key performance indicators (KPIs) to measure the global impact of the intervention from patient and nurse and organizational perspective.

Number of adverse events will be determined by counting the number of falls, catheter-associated urinary and bloodstream infections, pressure ulcers and restraints. These outcomes were chosen as they are considered important nursing outcomes in surgical and medical departments [22, 23]. Number of readmissions will be calculated for patients discharged and re-hospitalized in the same or different ward during the study period.

Patient's satisfaction, nurse's satisfaction and impact on nurse engagement and intention to leave will be assessed with specific surveys. The patient's satisfaction will be assessed through the CAHPS Hospital Survey [24]. This survey will be filled by the patient at discharge from the included ward. The nurse's satisfaction will be assessed through will be assessed through a single item, which asked nurses, "How satisfied are you with your current job?". Nurses could respond using a Likert scale ranging from "very satisfied" to "very unsatisfied" [25]. The impact on nurse engagement will be assessed through the Utrecht Work Engagement Scale [26]. This is a 3-item instrument (measuring the dimensions of vigour, dedication, and absorption) with response scale from 0 ("Not at all") to 6 ("Very much"). The total score can be calculated by averaging the responses of the items. Higher scores indicate greater work engagement. Intention to leave will be assessed by a single question asking respondents whether they intend to leave their current hospital within one year (possible answers will be yes/no) [25]. This survey will be filled by the nurse at a single time point during the data collection. All surveys where previously validated and used for other studies conducted by the research team [27, 28].

The number of reports and complaints will be assessed during the study period. All reports/complaints will be considered only if they will be referred to patients admitted during the study period. Reports/complaints will be considered if received at maximum two months after the end of the study period. Home discharges will be assessed as the number of discharges at home with / without home care. In this study, discharges at home will be interpreted positively, as the patient discharged at home will represent a lower occurrence of complications or complexity, compared to patients discharged to other facilities, other departments or who died.

Patients' needs will be assessed in terms of elimination, nutrition, mobility and therapeutic education. For each dimension, a mean of the assessments per day will be reported. For each patient's need, it will be collected the number of assessments per day, the number of interventions performed for resolving patient's care need per hospital stay and the number of patients achieving the care goal after receiving the intervention.

For each of these secondary outcomes, the related KPI will be calculated. The KPI will consider as denominator the total number of patients assessed or that received the intervention during the study period (Tabs. I, II).

Strategies to Minimize the risk of potential biases

To minimize the risk of selection bias, the inclusion and exclusion criteria specified in the protocol will be strictly adhered to. Reporting bias will be minimized by presenting all results obtained for primary and secondary outcomes, at least in the form of tables and/or figures. To reduce the risk of detection bias, blinding or masking of outcome assessors will be implemented. Thus, the statistician conducting the analyses will work on a blinded database (without indications regarding group membership) and will not be aware of the participants' group membership during the analyses.

Recruitment Procedure

A cohort will be identified through simple random sampling of EMRs from all patient discharges during the observation periods. A total of 450 records will be selected for each period (pre and post implementation) to determine the difference in the average length of stay between the two phases. The sample size calculation was based on the Wilcoxon–Mann–Whitney test, with

Tab. I. Description of outcome key performance indicator and related calculation method.

Outcome indicator	Description
Adverse events*+	Number of adverse events (falls, catheter-associated urinary and bloodstream infections, pressure injuries, restraints) / Total number of patients in the reference period
Readmissions*	Number of readmissions to the included ward / Total number of patients admitted during the reference period in the same ward
Patient satisfaction#	Number of satisfied patients / total number of patients in the reference period
Nurse satisfaction#	Number of satisfied nurses / total number of nurses
Impact on nurse engagement and intention to leave#	Number of nurses that demonstrate intention to leave / total number of nurses
Rate of home discharges*	Proportion of home discharges pre intervention / Proportion of home discharges post intervention
Reports and complaints§	Number of reports/complaints / total number of patients in the reference period

* Source: Electronic Health Records (Hospital Discharge Database), EMR. + Source: patient-reported incidents. # Source: BENE study survey. § Source: Public Relations Office.

Tab. II. Description of patient's needs key performance indicators and related calculation method.

Addressing of patients' needs	Documentation*	Interventions*	Achieved goals*
Elimination	Number of assessments documented by the team per day (if possible, identifying which member performed the assessment) / Total hospitalization days	Number of interventions prescribed by the team / Total number of patients requiring intervention prescription for the assessed need during the hospital stay	Number of patients achieving the goal after intervention by the team / Total number of patients receiving an intervention for the assessed need
Nutrition	Number of assessments documented by the team per day (if possible, identifying which member performed the assessment) / Theoretical total of assessments (3/day)	Number of interventions prescribed by the team (if possible, identify which member prescribed the intervention) / Total number of patients requiring intervention prescription for the assessed need during the hospital stay	Number of patients with the goal achieved after intervention by the team / Total number of patients receiving an intervention for the assessed need
Mobility	Number of assessments documented by the team (if possible, identifying which member performed the assessment) / Total hospitalization days	Number of interventions prescribed by the team (if possible, identify which member prescribed the intervention) / Total number of patients requiring intervention prescription for the assessed need during the hospital stay	Number of patients achieving the goal after intervention by the team / Total number of patients receiving an intervention for the assessed need
Therapeutic Education	Number of patients with documented assessments by the team (if possible, identifying which member performed the assessment) / Number of patients hospitalized in the reference period	Number of interventions prescribed by the team (if possible, identify which member prescribed the intervention) / Total number of patients requiring intervention prescription for the assessed need during the hospital stay	Number of patients achieving the goal after intervention by the team / Total number of patients receiving an intervention for the assessed need

* Suorce: EMR

80% power and a 5% level of significance. Based on these parameters, a total sample size of 900 patients (450 pre-intervention and 450 post-intervention) was deemed necessary to achieve adequate statistical power.

Data collection

Data regarding adverse events, readmissions, patient's needs and home discharges pre- and post-intervention will be collected from the integrated EMR and managed with a Case Report Form (CRF) prepared on the REDCap (Research Electronic Data Capture) platform hosted at the Ordine Mauriziano Hospital. REDCap is a secure, web-based application specifically designed to support data acquisition for research studies [29].

Only individuals officially registered as study investigators or those responsible for managing the REDCap application will receive authenticated access to the web platform and will upload/manage the data. Local investigators will be responsible for ensuring that the CRF is completed correctly and comprehensively.

Data will be retrospectively extracted through the facility's computerized system and anonymized by the facility to prevent the retrieval of sensitive patient data. The data collection form will be developed ad hoc and tested through an inter-rater reliability test. Local investigators involved in data collection from the EMR system will independently collect data from 10 complete patient records and compare the consistency of the

extracted data to ensure that the data collection form is a comprehensive and reliable tool.
Regarding patient satisfaction, nurse satisfaction, impact on nurse engagement, intention to leave and reports/complaints in the pre-intervention phase, data will be collected through a survey derived from other studies conducted by the research team [27, 28]. The wards of the Ordine Mauriziano Hospital involved in the current study participated in a national study on work well-being in 2022, the BENE study [27]. The BENE study required the participation of nurses and patients to a survey. The same variables will be assessed in the post-intervention phase, specifically data on nurse satisfaction, nurse engagement, and intention to leave the job, as well as patient satisfaction. In the post-intervention phase, data regarding nurses will be collected at a single time point during the 6-months of post intervention. The questionnaires are completely anonymous. Additionally, data on patient satisfaction will be collected by reviewing reports received by the Public Relations Office of the Ordine Mauriziano Hospital in Turin.

Data storage

All sensitive data collected will be stored in a server hosted by Ordine Mauriziano Hospital and will be accessible only by authorised investigators through the REDcap web platform. The extracted data will be available on local computer with limited access and protected by passwords and will be deleted at the end of the study.

Data analysis

The data collected will be analysed in an aggregated and anonymous form using descriptive and inferential statistics. The demographic characteristics of the sample and the levels recorded during the different assessments, before and after the intervention, will be described using descriptive indices such as mean and standard deviation or median with interquartile range (IQR). Additionally, the following statistical tests will be used (based on the type of data): 1) Student's t-test for independent samples or Wilcoxon-Mann-Whitney test to assess any differences between pre and post intervention for continuous variables; 2) Chi-square test (or non-parametric equivalent for non-normal distributions) to evaluate any differences between pre and post for categorical variables; 3) Student's t-test for paired data or Wilcoxon-Mann–Whitney test for intra-group evaluation of continuous variables. Multivariable regression models (*e.g.*, linear or logistic regression) will be considered to adjust for confounding factors (*e.g.,* patient's age and sex or ward) and to confirm the effect of the intervention on the outcomes.
Additionally, 95% confidence intervals of the mean lengths of stay stratified by medical or surgical departments will be provided. A significance level of 5% will be considered. To handle missingness of data, an analysis of the characteristics of the missing data will be carried out. Multiple imputation of these missing data will be implemented if appropriate [30]. Statistical analyses will be conducted with Jamovi V. 2.3.28 or similar software if necessary.

Ethical Considerations

This study will be conducted in full compliance with the international regulations [EU Directive 2001/20/EC], national regulation [Ministerial Decree 15 July 1997; Legislative Decree 211/2003; Legislative Decree 200/2007] regarding clinical trial and the principles of the Helsinki Declaration, to ensure the maximum protection of the participants. The study's promoter is committed to protecting sensitive personal data of the participants involved in the study as established by European regulations (EU GDPR 2016/679). All data will be treated to ensure participants' privacy according to current privacy regulations (EU GDPR 2016/679), and in any publications, data will be provided only in aggregated form. There are no compensations or reimbursements planned at any level. The principal investigator will have access to the system and will manage users and their credentials. Only specific users identified by the principal investigator will be able to access the data, and they will be assigned roles or permissions based on their needs. Each user will set a strong password (including uppercase and lowercase letters, numbers, and symbols).
This study has been approved by the Interhospital Territorial Ethics Committee "AOU Città della Salute e della Scienza di Torino." on 21st of May 2024 n°0067632. All deviations from the study protocol will be justified and reported to ensure transparency and integrity of the research.

Informed consent and data management

For the post-study, an informational leaflet and an informed consent form will be available in each included ward, explaining the study's structure, objectives, procedures, data collection, potential benefits of participation, and the absence of specific health risks, given that it involves an observational data collection. These details will be presented to interested individuals, who will have the freedom to sign informed consent and privacy statement for the processing of their data collected for the aims of this study.
An informational leaflet will be distributed to nurses, explaining the procedure and objectives of the study. Nursing staff will be asked to provide consent solely for completing the questionnaire and for the processing of data. These informational materials will be distributed to all nursing staff operating within the 3 facilities involved at the initiation of the study, and as new staff members are added throughout the study period.

Discussion

The FoC framework outlines all aspects involved in delivering safe, effective, and high-quality fundamental care [6]. Evidence continues to grow, showing that better hospital nurse staffing is associated with better

patient outcomes, including fewer hospital acquired infections, shorter length of stay, fewer readmissions, higher patient satisfaction, and lower nurse burnout [31]. The RN4CAST study recommended an average of six patients per nurse in hospital wards [32], and in this study the nursing staff will be adjusted following this recommendation to adequately implement the FoC framework.

The importance of this study lies above all in the intervention towards the satisfaction of the patient's needs (nutrition, mobilization, education and elimination), which previous literature has already shown to be linked to important outcomes with an impact on the healthcare system. Nutrition is an important subject of nursing care and one of the physical dimensions in the Fundamentals of Care framework. In addition, 82% of inpatients remain malnourished during their hospital stay and hospital malnutrition is associated with prolonged length of stay, increased hospital morbidity and mortality, high re-admission rates and low quality of life [33]. A systematic review [34] of randomized trials using early mobilization interventions showed decreased length of stay and improved functional status in older patients. Additionally, with early mobilization, 6 more patients every 100 were able to go home instead of nursing home or other care facility and hospital costs were reduced by $280 per patient per hospital stay. Therapeutic Patient Education has been found effective for improving numerous health and psychological outcomes in patients with chronic diseases [35]. On the other hand, to the best of our knowledge, to date no studies showed the association with adequate renal/bowel elimination management and patients' outcomes. Thus, this will be the first study to give insights on this topic. All these aspects will be assessed in this study, and the results will provide a concrete contribution to the scientific community regarding the improvements for patient outcomes by the Foc framework implementation in clinical practice.

Limitations

The first limitation of this study is that data collected through the EMR and uploaded on the CRF on REDcap web platform must be extracted by a local investigator with possible data entry errors. To minimize this limitation, a second local investigator will perform a cross-check on a random sample of data entered.

The second limitation of this study could be the amount of missing data. Even though the study is longitudinal some data measured on multiple time points could be missing.

A third limitation of this study lies in its quasi-experimental design, specifically the absence of a control group. This limits the internal validity of this study by reducing the ability to attribute outcome changes directly to the intervention and increasing the risk of selection bias. The presence of this bias will be assessed, and appropriate analysis will be performed to reduce this limitation.

Conclusion

This is the first protocol that will assess the outcomes of the implementation of the FoC framework. It will provide evidence on the effectiveness of the implementation of the FOC framework in the medical and surgical departments. The results provided by this study can be used as leverage for improving the response to the needs of the patient cared.

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Data availability statement

Not applicable.

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Ethics approval statement

This study has been approved by the Interhospital Territorial Ethics Committee "AOU Città della Salute e della Scienza di Torino" on 21st of May 2024 n° 0067632.

Conflict of interest statement

Nothing to declare.

Authors' contributions

All authors contributed to this manuscript. AB: Conceptualization, Methodology, Supervision, Writing-review & editing; GC: Investigation, Writing-original draft; SB: Investigation, Writing-review & editing; ADN: Investigation, Writing-review & editing; EG: Investigation, Writing-review & editing; OT: Investigation, Writing-review & editing; MS: Investigation, Writing-review & editing; AR: Investigation, Writing-review & editing; RS: Investigation, Writing-review & editing; GiC: Writing-original draft, Conceptualization, Methodology; LS: Conceptualization, Methodology, Supervision, Writing-review & editing.

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Non communicable diseases

The Effectiveness of Theory Based Educational Intervention on Health Literacy, Medication Adherence and Self-Manag

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Keywords

Health Literacy • Self-Care • Type 2 Diabetes • Medication Adherence • Education

Summary

Introduction
Theory-based educational interventions can play an important role in improving health literacy and promoting self-care behaviors and preventing diabetes complications. This study was conducted with the aim of investigating the effectiveness of educational intervention based on the Extended Theory of Planned Behavior on health literacy, medication adherence, self-care behaviors and metabolic indicators in T2D patients.
Methods
The present research was a Quasi-experimental study with a control group and measuring outcome variables at baseline and 3 months after the theory-based intervention. With multi-stage sampling, 112 patients with T2D referred to healthcare centers of Qazvin city were assigned to experimental and control groups equally. The intervention included six online group education along with educational video, pamphlets and 60 SMS reminders using strategies as role-playing, lecture, and scenario presentation. The data collection tools were: Demographic items, summary of diabetes self-care activities scale, short test of functional health literacy in adults, The Morisky 8-item medication adherence scale, Sub-Scales of extended TPB (36 items). Paired and independent t-test, chi-square, ANOVA and ANCOVA were used to data analysis.
Results
The mean of attitude, subjective norms, perceived behavioral control, action planning, coping planning, trust and the intention associated with health literacy and medication adherence increased significantly in the experimental group in the post-test by controlling the effect of the pre-test variable ($P < 0.001$). In addition, the results of ANCOVA showed the improvement in the total mean score of self-care and its dimension along with the meaning of FBS and HbA1c in the experimental group in the post-test ($P < 0.001$).
Conclusions
The focus of nurses and other medical staffs on improving health literacy, action & coping planning and psychological variables in the design of cognitive behavioral interventions can lead to improving self-care and medication adherence in T2D patients.

Introduction

Type 2 diabetes (T2D) is a chronic disease caused by various individual and environmental factors. Statistics emphasize the high prevalence of T2D as a major concern of healthcare systems and the main threat to the health of millions of people worldwide [1]. The estimation showed that 9.3% of adults aged 20-79 years worldwide have T2D, and on average, one out of every 11 adults might be diagnosed with diabetes [2]. In addition, almost two-thirds of people with diabetes do not reach treatment goals (HbA1c less than 7%) due to various reasons, such as non-adherence to the medication regimen or lack of adequate access to healthcare [3]. Therefore, a long-term increase in HbA1c (Glycated haemoglobin) and fasting blood sugar (FBS) levels have serious consequences, such as increasing the readmission rate, treatment costs, and premature mortality [4]. Moreover, non-communicable diseases cause almost three-quarters of deaths, and premature death from T2D has increased by approximately 5% between 2000 and 2016, despite the downward trend of non-communicable diseases [5]. Behaviors are the main factors affecting the health of T2D patients, and self-care plays an important role in controlling the short- and long-term consequences of T2D [6]. In addition, diabetes education is essential to improve self-care and reduce HbA1c. Moreover, the theoretical foundations and various strategies for educating T2D patients by nurses, midwives, and other healthcare workers (HCWs) have been increasingly strengthened in the past decade, and self-management education and empowerment have been recognized as an effective strategy for increasing self-care and reducing HbA1c [7]. However, nursing research and patient education studies have highlighted the low level of self-care behaviors, low participation in self-management and poor control of metabolic indicators in many T2D patients [3, 8, 9]. Many studies have confirmed the relationship between self-care behaviors and health literacy. In addition, there is a clear relationship between

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the ability to access, understand, and use information from different sources and health and disease status [10, 11].

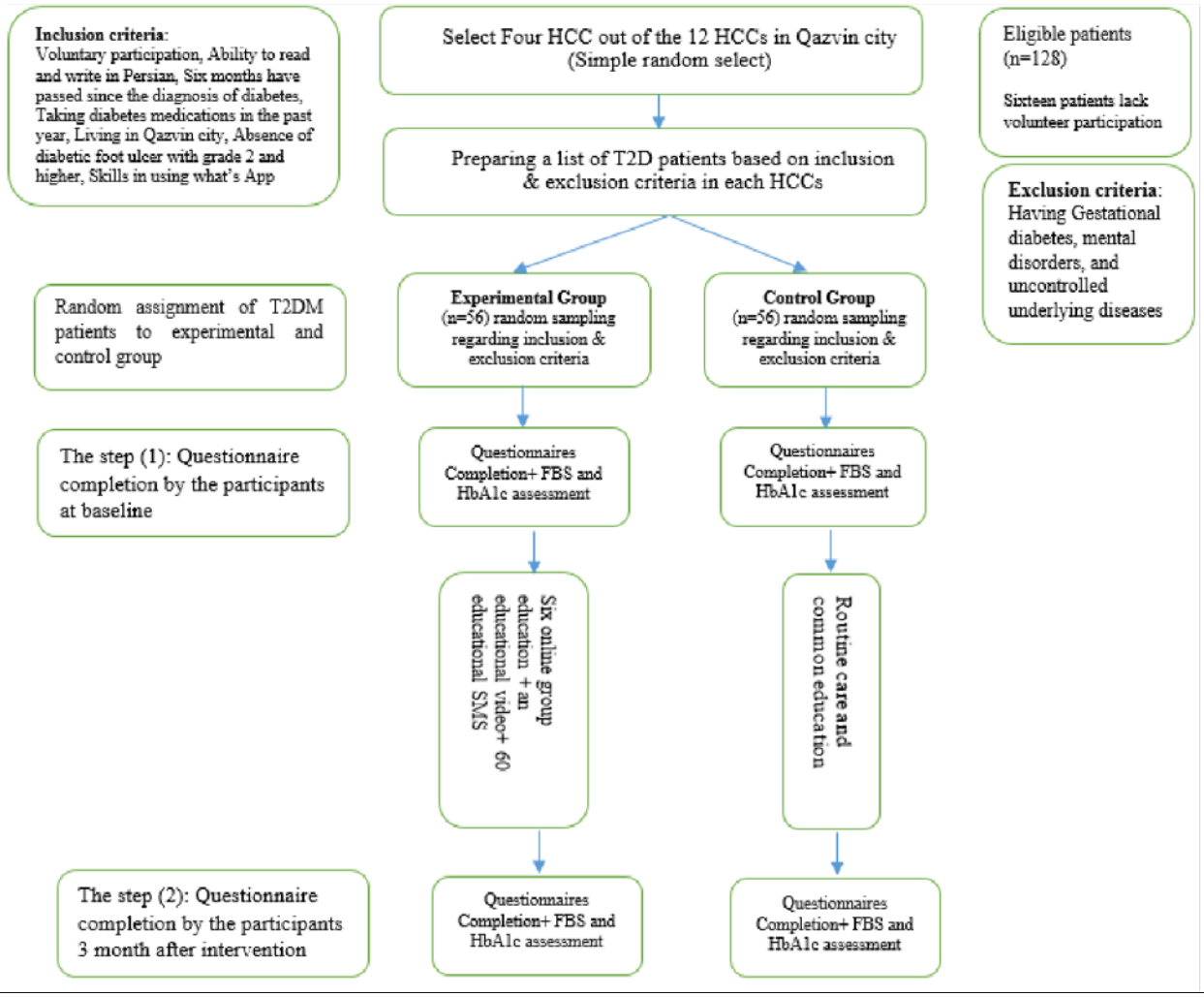
Health literacy refers to people's capacity to access, interpret, and understand basic information, which plays a fundamental role in making correct health decisions [12]. A low level of health literacy can lead to poor self-care behaviors such as lack of proper blood glucose monitoring and lack of ability to assess health status in general [13]. Unfortunately, despite the WHO's emphasis on the role of health literacy as a major determinant of health, many T2D patients do not have an optimal level of health literacy. For example, Mohammadi et al. (2015) emphasized that only 18.2% of T2D patients participating in the research had adequate health literacy skills, 11.8% had marginal, and 70.0% had inadequate health literacy skills [14]. Moreover, a review study by Momeni et al. (2020) showed that the mean score of health literacy in Iranian T2D patients is 56.65 and the status of health literacy in both sexes is not satisfactory [15]. In addition, Maleki Chollou et al. (2020) emphasized the low level of health literacy in T2D patients in Iran; health literacy and self-care behaviors described 80% of the variation in HbA1c [16]. Patients with different psychosocial characteristics may have different perceptions and beliefs about the educational programs provided by nurses or other medical staff, and the impact of such psychosocial variables on educational outcomes is often ignored [17] and as a result, one of the reasons for the failure of patients' education programs to achieve the desired level of behavior change can be the provision of the same educational content without considering psychological differences [18]. Additionally, the effectiveness of educational programs depends on the correct use of behavior change models by nurses, midwives, and other medical staff members. Choosing an appropriate behavioral change model is the first step in designing cognitive behavioral interventions [19].

A comprehensive and useful theoretical framework for discovering and changing factors affecting self-care behaviors in T2D patients is the Theory of Planned Behavior (TPB). Ajzen and Fishbein (1987) established this theory, considering its central role. Additionally, the design of the model based on value expectation theory can play an important role in explaining the factors related to health and social behaviors [20]. TPB has paid special attention to the contribution of effective involuntary and environmental factors in creating behavior in addition to individual voluntary factors [21, 22].

This model consists of attitude, subjective norms, perceived behavioral control (PBC), intention, and behavior, and predicts the occurrence of a specific behavior when the individual intends to perform it. This model is one of the most effective and comprehensive for describing the relationship between attitude and behavior [23]. The main assumption in this theory is that intention is the main predictor and influencing variable on behavior, and includes the desire, planning, and intention to perform the behavior. Intention, in turn, is influenced by other constructs, including attitudes, subjective norms, and PBC. Attitude is the result of a person's assessment of the positive and negative consequences of performing a behavior and refers to the general feeling of liking and disliking a certain behavior. The more favorable the attitude towards a behavior, the more likely a person is to perform that behavior. The subjective norm also refers to a person's belief about the influence of significant others; in other words, it reflects the degree to which a person perceives approval and disapproval for performing a behavior from significant others, such as family members, colleagues, and close friends. For example, if the patient imagines that nurses and other medical professionals approve of self-care behaviors, the probability of continuing certain behaviors will be higher. PBC refers to the fact that a person feels that the desired behavior is under their voluntary control; in other words, the perceived difficulty or ease of a certain behavior is reflected in these constructs [21, 22, 24]. Previous studies have emphasized the effectiveness of TPB in explaining the psychosocial variables affecting self-care behaviors in T2D patients [25-27]. For example, Pan et al. (2023) showed that attitude, subjective norms, and PBC were strong predictors of intention, whereas intention and PBC had a direct effect on self-care behaviors [26]. Moreover, the relationship between behavioral intention and exercise, blood glucose monitoring, and foot care was also confirmed in a study by Lin et al. (2020) [27]. In addition, many studies have shown that interventions based on TPB lead to improvements in self-care behaviors and health literacy in T2D patients [14, 28-31]. For example, Kazemi and Rahmati (2021) found that T2D patients' lifestyles improved after participating in a theory-based educational program associated with motivational interviewing [30]. The improvement in preventive nutritional behaviors and TPB constructs after participating in a 6-week educational workshop based on TPB was also confirmed by Maleki et al. (2016) [31]. Despite the efficiency and effectiveness of TPB in predicting and changing self-care behavior in T2D patients, this theory has been criticized by some researchers [32, 33]. For example, some researchers believe that TPB often ignores the emotional aspects of attitudes and considers only logical and cognitive factors. In addition, the amount of variance predicted by TPB constructs can be significantly improved by adding new psychological variables. In other words, the relationship between intention and behavior can be influenced by other variables. For example, White et al. (2012) showed that an educational intervention based on extended TPB led to more short-term improvements in physical activity in T2D and cardiovascular patients, and adding a planning construct can make a significant contribution to improving training outcomes [32]. Ferreira et al. (2017) also emphasized the improvement of the potential of predicting the variance of physical activity after adding trust in the physician, action, and coping planning to the TPB framework [33].

Therefore, considering the increasing prevalence of T2D and the serious consequences resulting from it,

Fig. 1. Consort diagram of research stages.



the efficiency of theory-based educational interventions in improving self-care behaviors and health literacy, and the necessity of familiarizing nurses with the design of theory-based interventions, the present study was conducted with the aim of investigating the effectiveness of the educational intervention based on the Extended Theory of Planned Behavior on health literacy, medication adherence, self-care, and metabolic indicators in T2D patients with in Qazvin city.

Materials and Methods

Study type

The current research is a quasi-experimental study aimed at measuring self-efficacy, self-care behaviors, and metabolic indicators (FBS and HbA1c) in T2D patients (experimental and control groups) in Qazvin city before and three months after the theory-oriented educational intervention, conducted between June 2021 and March 2022.

Participant, sample size and sampling process

The research population included all patients with type 2 diabetes receiving healthcare and covered by healthcare centers in Qazvin city. The sample size required to conduct the previous study was calculated based on previous studies [14, 28], according to a 95% confidence level, 80% power, and an effect size of 0.45, and 112 patients with type 2 diabetes were randomly and equally assigned to the experimental and control groups. To select the participants, four healthcare centers (HCC) were selected from all HCC of Qazvin city by simple random sampling, and then registered nurses based on the inclusion and exclusion criteria prepared a list of T2D patients in each center. In the next step, patients were assigned to one of the experimental or control groups using a table of random numbers. The steps for assigning patients to the study groups are shown in a consort diagram (Fig. 1).

Inclusion and exclusion criteria

The entry criteria were voluntary participation, ability to read and write in Persian, age between 18 and 60

years, at least six months since the definitive diagnosis of type 2 diabetes, history of drug treatment, willingness to receive nursing care and treatment at home, living in Qazvin city, and actively visiting HCCs for at least one year. Not suffering from diabetic foot ulcer (grade 2 or higher based on Wagner's diagnosis criteria and endocrinologist confirmation) and the ability to use WhatsApp application. In addition, the exclusion criteria were as follows: returning incomplete questionnaires or refusing to answer all items, non-participation in part of training sessions (less than 50% of sessions), unwillingness to test blood glucose and HbA1c, uncontrolled underlying diseases such as uncontrolled hypertension (90/160 mmHg) despite taking medication, suffering from severe diseases or disabilities such as blindness, limb amputation, cardiovascular diseases, respiratory disorders, brain damage, and kidney failure leading to dialysis, and finally using any type of psychoactive drugs (except insulin drugs).

Intervention plan and content

In addition to routine patient education, an educational program based on the extended TPB was prepared, and an expert panel approved its scientific content validity. Routine education includes short-term, face-to-face, in-person, and daily training provided by healthcare personnel to remind them of the importance of self-care. This program included six online group training sessions (approximately 45 minutes). The groups consisted of 6 to 9 patients, and the educational sessions were held weekly. The hours and days of online training sessions were provided to each of the participants by two text messages: one day and one hour before the training sessions. The content of the educational sessions was compiled according to the extended TPB constructs and the evaluation of the answers to the questionnaires collected from the first stage. Based on the objectives of each session, several educational strategies, including lectures, group discussions, question-answers, role-playing, and brainstorming, were used to transfer information, change beliefs, and promote behavior. At the same time, to remember the contents of the sessions, two short educational video clips (7 minutes) along with two targeted pamphlets were given to the experimental group. Online group training was conducted on whatsApp, and a free internet package (5 GB) was given to each patient to increase participation in online sessions. Moreover, 10 educational messages were designed for each session to remember the content of each session in one-week intervals between online sessions. In addition, in the final phase of the study and after completing the questionnaire, all patients in the experimental and control groups were given a certificate of participation in the research, along with a pocket calendar and a stationery package as a gift. The contents of the educational sessions are presented in Table I.

Data Collection Instruments

The patients with T2D in two groups completed the data collection tools, which included a multi-part questionnaire and a clinical assessment of metabolic indexes as FBS and HbA1c, before and 3 months after the educational intervention. The research tools were:

1. Demographic and medical history items include age, gender, economic status, marital status, education level, family history of diabetes, BMI (body mass index), and employment status.
2. Fasting blood sugar (FBS) and Glycated hemoglobin A1C (HbA1c): These indicators were measured based on the guidelines for measuring FBS and HbA1c of the Iranian Ministry of Health and Medical Education regarding 8 hours of fasting [34].
3. Summary of Diabetes Self-Care Activities (SDSCA), which consisted of 15 questions about diet, physical activity, blood sugar monitoring, foot care, and medication use. Each question was scored from 0 to 7 in terms of the number of days the person performed self-care behaviors in the past week. The total score ranges from 0 to 56 and is divided into three levels: unfavorable (0-16), somewhat favorable (17-32) and favorable (33-56). In addition, the final scores for physical activity and blood sugar control were classified into three levels: unfavorable (0-2), somewhat favorable (3-4) and favorable (5-7). Three questions were used to assess foot care behaviors, and the range of scores was 0–21, classified into unfavorable (0-6), somewhat favorable (7-12) and favorable (12-21) levels. Finally, two questions were used to assess medication adherence. The scores in this section range from 0 to 14, which is divided into three levels: unfavorable (0-4), somewhat favorable (5-8) and favorable (9-14). The total self-care score was divided into the following levels: poor self-care (0-37), moderate self-care (38-71), and good self-care (72-105). The psychometric properties of the mentioned scale have been confirmed in the previous studies [35, 36].
4. Short Test of Functional Health Literacy in Adults (S-TOFHLA): This questionnaire is one of the most comprehensive general standard tools for evaluating health literacy. It consists of 33 questions, with the first 27 answered based on a 5-point Likert scale from 1 (never) to 5 (always). The remaining 7 items are answered using a Likert scale from completely easy to completely difficult. The questionnaire includes five dimensions as follows: reading (6 items), access to information (6 items), understanding (6 items), appraisal (6 items), and decision making (9 items). The final health literacy score ranges from 33 to 165. The total mean score is divided into three levels: insufficient literacy (33-77), marginal literacy (78-122), and adequate health literacy (123-165). The validity and reliability of the S-TOFHLA have been emphasized in previous Iranian studies [37, 38].
5. The Morisky 8-Item Medication Adherence Scale (MMAS-8): The MMAS-8 has 8 items and is scored based on the Likert scale (yes and no). The range of total scores for this scale is between 0 and 8, with a higher total score indicating better medication adherence. The validity and reliability of this scale have been confirmed among patients with T2D in Iran [39-41].

Tab. I. Educational content, goals and strategies based on the extended TPB for experimental group.

No	Title of Session	Objective	Educational Strategies	Learning Assist Materials
First session	Type 2 diabetes, Self-care and Medication Adherence	Definition & Symptoms of T2D Mechanism of T2D development Complications of T2D T2D risk factors Importance of Medication Adherence	Lecture and Question & Answers	Slide Show, Pamphlet, Booklet, Reminder Messages
Second session	Self-care and its role in controlling the consequences of diabetes	Normal blood glucose and its measurement Foot care methods Types of physical activity Healthy diet and calorie intake Compliance with the prescribed medication and physician prescriptions	Lecture, Role Playing, Question & Answers	Video & Photo Show, Slide Show, Pamphlet, Booklet, Reminder Messages
Third session	Attitude change	Severity of T2D consequences The ability to control T2D with self-care The importance of foot care Various risks regarding unhealthy eating Sensitivity of each patient Mortality and terrible long-term outcomes	Lecture, Group Discussion, Scenario Presentation	Educational Movie (5 Minute) + Brochure and Booklet, Reminder Messages
Fourth session	Barriers, benefits and Self-efficacy promoting	personal and environmental barriers providing different solutions Strengthening social support Practical demonstration of self-care skills Verbal feedback and persuasion	Group Discussion + Role playing along with Question & Answer	Slide Show, Pamphlets, Reminder Messages
Fifth session	Action & coping planning	Goal setting Setting up a plan to overcome time, place and skill barriers Strengthening Self-regulation Planning to access information, experts, etc.	Short Lecture + Individual consultation	Brochure, Reminder Messages
Sixth session	Feedback and behavior enforcing	Self-monitoring and strengthening beliefs Internal control and encouraging problem analysis Offering different individual solutions Assessing individual needs and identifying and resolving irrational feelings and strengthening individual insight	Short Lecture + Individual consultation	Brochure, Reminder Messages

6. Sub-Scales of extended TPB: F) Sub-Scales of Extended TPB: According to the guidance of Ajzen (2016) [20], a semi-structured interview with 10 patients with T2D was conducted to extract silent beliefs related to the TPB constructs, and the initial version of the scales was designed based on these extracted beliefs. An expert panel evaluated the face and content validity of the questions, and the content validity index (CVI) and content validity rate (CVR) were confirmed. In the next step, the subscales of the extended TPB were distributed and completed by a sample of 12 T2D patients over an interval of 15 days to determine test-retest validity. Additionally, Cronbach's alpha coefficient was used to assess the internal consistency of each construct. Finally, the following sub-scales were used to measure the constructs related to the extended TPB: The Subjective Norms Scale consists of 4 items, where patients were asked to respond to each item on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). The range of answers was between 4 and 20, with higher mean scores indicating stronger social support and social norms for self-care. A Cronbach's alpha coefficient of 0.85 indicates good internal consistency, and a test-retest coefficient of 0.92 also confirms the reliability of the subjective norms. The Attitude Scale consists of 8 items measured on a 5-point Likert scale from 1 (completely disagree) to 5 (completely agree). The range of scores was between 8 and 40, with lower scores indicating a poor attitude and vice versa. Furthermore, the internal consistency and acceptable reliability of this scale were confirmed by Cronbach's alpha coefficient ($\alpha = 0.81$) and test-retest coefficient ($r = 0.84$). The Perceived Behavioral Control Scale consists of 6 items answered on a 5-point Likert scale from 1 (not at all sure) to 5 (completely sure). The range of answers varied from 6 to 30, with a higher score indicating greater control and the patients' perceived ability to perform the desired self-care behaviors. Moreover, the internal consistency and reliability of this scale were confirmed by Cronbach's alpha coefficient ($\alpha = 0.86$) and test-retest coefficient ($r = 0.89$). The Behavioral Intention Scale consisted of 5 questions, and patients were asked to respond on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). Scores ranged from 5 to 25, with a lower score reflecting weaker intention and vice versa. The psychometric properties of the mentioned subscale were also confirmed in the pilot study ($\alpha = 0.82$, $r = 0.90$). Action and Coping Plan Scales: To evaluate

Tab. II. Comparison of demographic characteristics between experimental and control groups before the theory based educational intervention.

Variables	Group	Control Group Mean ± SD	Experimental group Mean ± SD	P-value
Age (Year)		51.3 ± 13.2	49.7 ± 11.5	0.26
BMI (kg/m^2)		28.32 ± 3.73	27.95 ± 3.68	0.23
History of Disease		8.58 ± 7.36	9.46 ± 7.11	0.34
Variables		**Control Group Frequency (%)**	**Experimental group Frequency (%)**	**P-value**
Gender	Male	21 (37.50)	19 (33.93)	0.58
	Female	35 (62.50)	37 (66.07)	
Employment status	Employed	25 (44.64)	24 (42.86)	0.46
	Housewife	24 (42.86)	27 (48.21)	
	Unemployed	7 (12.50)	5 (8.93)	
Marital Status	Married	49 (87.50)	51 (91.7)	0.85
	Single, divorced, etc.	7 (12.50)	5 (8.93)	
Educational Status	Elementary & middle school	9 (16.07)	11 (19.64)	0.72
	High school & Diploma	27 (48.21)	16 (28.57)	
	University	20 (35.71)	19 (33.93)	
Family History of T2D	Yes	30 (53.57)	28 (50.0)	0.41
	No	26 (46.42)	28 (50.0)	
Treatment Type	Hypoglycemic drugs	27 (48.21)	26 (46.42)	0.18
	Insulin	14 (25.0)	16 (28.57)	
	Hypoglycemic drugs+ Insulin	15 (26.79)	15 (26.79)	

action planning and coping planning, a 9-item scale was used (action planning with 5 items and coping planning with 4 items). Patients were asked to respond to questions using 5-point response options. The range score for the action planning scale was between 5 and 25, while the coping planning scale ranged from 4 to 20. The psychometric validity of this scale has been confirmed in previous studies [14, 42, 43]. Trust Scale: Trust in treatment methods and healthcare providers was evaluated using a 4-item scale. Patients were asked to respond to the questions of this scale using 5-point Likert response options. The range of responses was between 4 and 20, with higher scores indicating deeper trust in treatment methods and healthcare professionals, and vice versa. This scale has been used in many studies, and its psychometric properties have also been confirmed [44, 45].

Questionnaires were administered to the experimental and control groups at the training office of healthcare centers, and they were asked to answer the questions in approximately 45 minutes. A member of the research team was present while the questionnaires were completed to address any questions, explain how to fill out the instrument, emphasize the importance of providing honest answers, and ensure that all questions were answered.

Ethical considerations

The Ethics Committee of Qazvin University of Medical Sciences approved the present study (IR.QUMS.REC.1400.179). Additionally, all participants were informed about their voluntary participation in the research, and all of them signed the voluntary participation form. Furthermore, all patients were reminded that the questionnaires are anonymous and do not contain tracking codes, and all information will remain confidential with the research team. The information will be provided to health authorities in the form of a general report.

Statistical analysis

The data was entered into SPSS 25.0 and the normality of the data distribution was confirmed by the Kolmogorov-Smirnov test. Statistical tests such as paired and independent t-tests, chi-square tests, one-way analysis of variance (ANOVA), and analysis of covariance (ANCOVA) were used for data analysis. The significance level in the current study was considered less than 0.05.

Results

The mean age of patients participating in the present study was 50.8 ± 12.7 years, and 64.29% of the patients were female. In addition, 43.75% were employed, 89.29% were married, and more than 83.0% had poor to moderate economic status. The statistics showed that 51.76% had a family history of illness, and 34.82% had a university education. The demographic characteristics of the patients were compared between the experimental and control groups, and the results showed that there was no statistically significant difference between the two groups in terms of the mentioned variables before the educational intervention. Other details has showed in Table II.

The comparison of the means of the Extended TPB

Tab. III. Covariance analysis of the effect of the educational intervention on constructs of the Extended Theory of Planned Behavior in the experimental and control groups.

Variables	Sources	Type III sum of Squares	df	Mean Square	F	p-value	η^2
Attitude	Pretest	2533.52	1	2533.52	128.45	0.000	0.74
	Group	432.47	1	432.47	24.36	0.001	0.43
Subjective Norms	Pretest	142.30	1	142.30	61.45	0.000	0.67
	Group	20.285	1	20.28	9.61	0.003	0.42
PBC	Pretest	776.37	1	776.37	284.74	0.000	0.78
	Group	164.26	1	164.26	162.35	0.000	0.54
Action planning	Pretest	379.12	1	379.12	122.65	0.000	0.71
	Group	142.16	1	142.16	53.21	0.000	0.49
Coping Planning	Pretest	213.87	1	213.87	98.37	0.003	0.40
	Group	108.33	1	108.33	26.44	0.000	0.38
Trust	Pretest	1922.65	1	1922.65	119.83	0.000	0.61
	Group	336.55	1	336.55	29.69	0.002	0.41
Intention	Pretest	862.44	1	862.44	145.75	0.001	0.59
	Group	203.51	1	203.51	83.42	0.000	0.54

Tab. IV. Covariance analysis of the effect of the educational intervention based on the extended TPB on self-care and its dimensions in the experimental and control groups.

Self-Care Dimensions	Sources	Type III sum of Squares	df	Mean Square	F	P-value	η^2
Regular Physical Activity	Pre-Test	215.36	1	215.36	232.45	0.001	0.18
	Group	75.63	1	75.63	35.16	0.000	0.39
Healthy Diet	Pre-Test	460.26	1	460.26	173.27	0.000	0.10
	Group	149.5	1	149.5	41.33	0.433	0.21
Foot care	Pre-Test	1008.48	1	1008.48	213.36	0.000	0.01
	Group	20.57	1	20.57	12.55	0.002	0.41
Medication Adherence	Pre-Test	1123.52	1	1123.52	164.50	0.000	0.11
	Group	32.43	1	32.43	10.89	0.254	0.48
Blood Sugar Control	Pre-Test	1417.36	1	1417.36	178.81	0.000	0.16
	Group	72.90	1	72.90	27.34	0.108	0.37
Total Score	Pre-Test	944.83	1	944.83	127.5	0.000	0.38
	Group	194.36	1	194.36	31.07	0.001	0.65

constructs is shown in Table III. The results indicate that the mean of attitude ($F = 24.36$, $p = 0.001$), subjective norms ($F = 9.61$, $p = 0.003$), PBC ($F = 162.35$, $p < 0.001$), action planning ($F = 53.21$, $p = 0.001$), coping planning ($F = 26.44$, $p = 0.001$), trust ($F = 29.69$, $p = 0.002$), and intention ($F = 83.42$, $p < 0.001$) increased significantly in the experimental group in the post-test while controlling for the effect of the pre-test variable. Additionally, η^2 showed that 43.6%, 42.2%, 54.3%, 49.2%, 38.6%, 41.1%, and 54.2% of the changes in attitudes, subjective norms, PBC, action planning, coping planning, trust, and intention were explained by the theory-based educational intervention.

Table IV shows the results of ANCOVA related to the effect of a theory-based educational intervention on self-care dimensions in T2D patients. After controlling for the effect of the pre-test, the results of ANCOVA indicated significant differences in mean scores for regular physical activity ($F = 35.16$, $P < 0.001$), healthy diet ($F = 41.33$, $P < 0.001$), food care ($F = 12.55$, $P < 0.001$), medication adherence ($F = 10.89$, $P < 0.001$), blood sugar control ($F = 27.34$, $P < 0.001$), and the total mean score of self-care ($F = 31.07$, $P < 0.001$) in the post-test. Additionally, the η^2 values showed that the theory-based educational intervention accounted for 39.8%, 21.9%, 41.5%, 48.2%, 37.7%, and 65.5% of the variance in regular physical activity, healthy diet, food care, medication adherence, blood sugar control, and total self-care in T2D patients, respectively.

The results of the independent t-test and the comparison of the means of FBS and HbA1c between the experimental and control groups before the theory-based intervention showed that there was no significant difference between the two groups in terms of the mentioned variables. Nevertheless, the mean of FBS (from 166.7 ± 51.50 to 122.4 ± 47.6) and HbA1c (from 7.88 ± 1.85 to 6.23 ± 1.37) decreased significantly after the education in the experimental group. Moreover, the results in Table V emphasized that the mean scores of health literacy (from 67.25 ± 22.15 to 119.50 ± 38.7) and medication adherence (from 3.37 ± 2.05 to 5.94 ± 3.14) in the experimental group increased significantly after the theory-based educational intervention.

Tab. V. The results of educational intervention based on the extended TPB on HbA1c and FBS level in the experimental and control groups.

		Before Education	After Education	
Metabolic indexes	Group	Mean ± SD	Mean ± SD	P-value
FBS	Control	172.6 ± 49.25	166.5 ± 50.3	0.21
	Experimental	166.7 ± 51.50	122.4 ± 47.6	P < 0.001
	**p_{value}	0.42	P < 0.001	
HbA1c	Control	8.05 ± 1.81	7.94 ± 1.86	0.553
	Experimental	7.88 ± 1.85	6.23 ± 1.37	P < 0.001
	**p_{value}	0.63	P < 0.001	
Health Literacy	Control	71.46 ± 25.63	74.87 ± 26.5	0.32
	Experimental	67.25 ± 22.15	119.50 ± 38.7	P < 0.001
	**p_{value}	0.28	P < 0.001	
Medication Adherence	Control	3.12 ± 1.68	3.46 ± 2.18	0.315
	Experimental	3.37 ± 2.05	5.94± 3.14	P < 0.001
	**p_{value}	0.42	P < 0.001	

Tab. VI. Covariance analysis of the effect of the educational intervention based on the extended TPB on medication adherence and health literacy in the experimental and control groups.

Variables	Sources	Type III sum of Squares	df	Mean Square	F	P-value	η^2
FBS	Pretest	4823.28	1	4823.28	63.81	0.000	0.10
	Group	1511.01	1	1511.01	12.35	0.002	0.42
HbA1c	Pretest	1524.31	1	1524.31	84.57	0.000	0.16
	Group	372.26	1	372.26	21.55	0.000	0.67
Health literacy	Pretest	1288.25	1	1288.25	90.13	0.000	0.19
	Group	512.60	1	512.60	14.65	0.035	0.3
Medication Adherence	Pretest	1739.62	1	1739.62	52.86	0.000	0.21

The results of the ANCOVA showed that the mean of FBS ($F = 12.35$, $P < 0.001$) and HbA1c ($F = 21.55$, $P < 0.001$) in the experimental group decreased significantly after the intervention while controlling for the effect of the pre-test. Additionally, the covariance results listed in Table VI indicated that the mean score of health literacy ($F = 14.65$, $P < 0.001$) and medication adherence ($F = 18.52$, $P < 0.001$) in the experimental group improved significantly after controlling for the effect of the pre-test. The results of the ANCOVA showed that the mean of FBS ($F = 12.35$, $P < 0.001$) and HbA1c ($F = 21.55$, $P < 0.001$) in the experimental group decreased significantly after the intervention while controlling for the effect of the pre-test. Additionally, the covariance results listed in Table VI indicated that the mean score of health literacy ($F = 14.65$, $P < 0.001$) and medication adherence ($F = 18.52$, $P < 0.001$) in the experimental group improved significantly after controlling for the effect of the pre-test.

Discussion

The present study was conducted to determine the effect of an educational intervention based on the extended Theory of Planned Behavior (TPB) on self-care behaviors, health literacy, medication adherence, and metabolic indicators of people with Type 2 Diabetes (T2D) in Qazvin city. The results generally show a significant improvement in the mentioned variables after the theory-based educational intervention in the experimental group.

One of the most important findings of this study was the promotion of psychological variables related to the extended TPB after the educational intervention in the experimental group, which aligns with the findings of previous studies [46, 47]. For example, Riangkam et al. (2021) demonstrated that theory-based self-care education delivered via mobile phones increased the knowledge and awareness of T2D patients, leading to improvements in psychological predictors such as attitude, social support, and self-efficacy [46]. Additionally, the results of Aliabad et al. (2014) revealed the preservation of physical activity capacity in coronary heart patients, along with improvements in psychological constructs related to the Health Action Process Approach (HAPA) model in the experimental group after participating in the theory-based educational program that promoted family support [47]. It seems that providing simple and comprehensible information about the relationships between self-care behaviors and controlling the consequences of diabetes, along with their repetition in the form of Short Message Service (SMS), has increased patients' awareness of self-care behaviors.

Also, the emphasis of cognitive behavioral interventions – routinely provided by nurses or other personnel in hospitals or health centers – should be on the importance of assessing the benefits and barriers of self-care in T2D patients. Online training can be effective in strengthening

behavioral intention and improving self-management in patients with diabetes by clarifying the social, physical, and psychological consequences of diabetes and providing frequent and diverse constructive feedback through internet networks and mobile phones.

The results of the current research indicated that the means of trust, action, and coping planning in the experimental group improved significantly after the theory-based intervention, which was consistent with the findings of Aliabad et al. (2022) [47], Labudek et al. (2022) [48], Schroé et al. (2022) [49], and Daryabigi et al. (2021) [50]. The findings of Labudek et al. (2022) showed that the implementation of a group theory-based educational intervention, along with the improvement of psychological determinants, especially action planning and coping planning, ultimately led to positive changes in lifestyle, improved physical activity status, and prevention of falls in the elderly [48]. In the present study, trust, action, and coping planning were added to the TPB to strengthen the potential to describe the variance of self-care behavior. Planning is a prospective self-regulatory strategy that connects individual responses and anticipated situational guiding factors. Planning regarding the time, place, and method to achieve the main goals facilitates the realization of behavioral objectives [49]. Nurses and HCWs can reduce the gap between intention and behavior by focusing on improving self-regulation skills and encouraging the audience to consider the conditions and context in which self-care behaviors occur [51]. Goal setting, describing complete behavioral goals, outlining the necessary actions to achieve the goals, determining the necessary resources—equipment and time, establishing criteria and methods for measuring progress, and providing diverse practical solutions to address possible obstacles were part of the strategies used in theory-based educational sessions to strengthen "action planning" and "coping planning." Mirzaei et al. (2020) emphasized the improvement of health literacy and nutritional performance of the elderly with diabetes after a theory-based educational intervention [52]. Additionally, Hejazi et al. (2018) emphasized the increase in self-efficacy, self-care, and health literacy scores following a theory-based educational intervention [53]. The relationship between low levels of health literacy and poor self-care behaviors in T2D patients has been confirmed in many studies [54]. In other words, patients need to receive correct and valid information from various channels, such as nurses, HCWs, or social media, to understand their condition and cooperate in self-care programs. In fact, patients' skills to obtain, correctly understand, and apply this information will significantly impact their behavior and health status [55]. Furthermore, patients with insufficient health literacy have poorer health status, a higher rate of hospital admissions, and require more nursing care. Nursing reports indicate that the death rate among these patients is almost twice as high as that of other chronic patients [56]. A review of educational interventions shows that educational methods and materials have been chosen in a way that is more suitable for learners with sufficient health literacy, while clients with insufficient health literacy do not benefit much from these interventions [17]. Learning theories emphasize that without considering the characteristics of the target audience in health education interventions, especially their level of health literacy, it is not possible to bridge the learning gap between individuals with sufficient and insufficient health literacy [18]. Therefore, cognitive-behavioral interventions should pay special attention to assessing the status of patients based on their health literacy level and designing educational interventions according to their psychological stages of readiness for change and the level of health literacy and awareness.

In line with the findings of previous research [28, 57-59], the results of the present study showed improvement in FBS and HbA1c levels in experimental group patients after a theory-based educational intervention. For example, Beiranvand et al. (2015) demonstrated that the mean score of attitudes towards foot care performance in the experimental group improved significantly after an educational intervention based on TPB [58]. Moreover, Hosseini et al. (2021) determined that, along with the improvement in retinopathy prevention, the mean FBS and HbA1c levels in the experimental group were significantly reduced after the theory-based educational intervention [28]. It seems that displaying practical strategies, along with role-playing and providing efficient feedback while improving patients' self-efficacy, had positive effects on reducing FBS and HbA1c and increasing self-care behaviors in T2D patients. The main goal of treating patients with diabetes is to achieve optimal control (HbA1c less than 7%), which is related to the reduction of morbidity and mortality. Additionally, considering that a 1% increase in this variable causes a 12% increase in coronary artery diseases, the reduction of this index should be prioritized by nurses and HCWs in various counseling programs and cognitive-behavioral interventions. Clinical indicators such as HbA1c and FBS have a significant relationship with LDL, HDL, BMI, and the amount of physical activity, and incorporating a regular physical activity program and weight loss program can significantly enhance the effectiveness of interventions.

The improvement of medication adherence in the experimental group after the intervention was another finding of the present study, which was consistent with the results of the study by Dashtian et al. (2018) [60] and other studies [61-64]. For example, Razavi et al. (2017) showed that the educational intervention based on the AIM model led to an increase in knowledge, motivation, and ability, as well as a decrease in HbA1c and an increase in the mean of medication adherence [63]. Additionally, the findings of the Zamani et al. (2020) study confirmed the improvement of medication adherence after five sessions of group training based on the Extended Parallel Process Model [64]. The findings of Tajari et al. (2019) also confirmed the effect of the SMS and Telegram reminder system on diet compliance among adolescents with type 1 diabetes [61]. When patients adhere to the treatment and the recommendations of the nurses who

have the necessary information, they possess enough motivation to control the disease. On the other hand, the patient's thorough understanding of the treatment process is a fundamental condition for voluntary medication adherence. Therefore, educational programs should provide the foundation for improving self-care behaviors and medication adherence by changing entrenched beliefs about the importance of continuing treatment, strengthening self-efficacy in relation to controlling the disease's consequences, and increasing health literacy and health awareness.

The change in self-care behaviors in T2D patients after the theory-based educational intervention is considered the most important finding of the current research, which is consistent with the results of previous meta-analyses [65, 66]. The meta-analysis by Zhao et al. (2017) showed that educational interventions designed based on one or more theories were able to improve HbA1c, self-efficacy, diabetes knowledge, and self-care [65]. Zare et al. (2020), after a systematic review of 20 studies, concluded that educational interventions based on behavior change models such as the health belief model, empowerment theory, precede-proceed model, and theory of planned behavior were able to change awareness and attitude, and improve self-care skills in T2D patients [66]. Additionally, the improvement of psychological constructs along with the promotion of self-care behaviors after the educational intervention based on the theory of reasoned action was confirmed by Babazadeh et al. (2017) [67]. Furthermore, the findings of the study by Hajipour et al. (2022) also showed a significant decrease in the mean of FBS and HbA1c, as well as an improvement in self-care behaviors after an intensive educational intervention based on the transtheoretical model [68]. Moreover, the findings of Ebadi Fardazer et al. (2017) showed a significant increase in the mean total score of self-care and all its domains in the 2 and 3 months following the educational intervention based on the locus of control in T2D patients [35]. Understanding exactly what factors can increase the success rate of patients in the path of behavior change is considered a basic concern of many studies [17, 18]. Most motivational and self-regulation theories emphasize that the identification and accurate determination of psychological variables affecting behavior is a fundamental step in designing interventions, and insufficient attention to this will reduce the effectiveness of interventions [51]. Patients may have different plans to control the disease and may unconsciously use various strategies, but the unplanned use of coping strategies to manage temptations and various social pressures, or insufficient motivation due to low self-efficacy, ultimately reduces the level of self-care [18, 19]. Improving health literacy, strengthening positive beliefs, encouraging self-efficacy, and enhancing the social support network have positively influenced the psychological readiness of patients to accept the necessity of change and to initiate the process of behavior change.

This research faced several limitations: first, the findings were compared with only one control group, which limits the researchers' ability to judge the effectiveness of the educational intervention in comparison with other behavior change models. Therefore, it is recommended that nursing researchers design the study based on traditional education groups and education based on other behavior change models or patient education based on web-based strategies, etc. Secondly, the final goal of the present study was to change self-care behaviors. A set of behaviors whose change through theory-based educational intervention requires the design of targeted educational content and a relatively long time for training, as well as the use of expert nurses or HCWs to manage the training courses. It is evident that focusing on specific and limited behavior in the design of educational interventions, such as regular insulin injections or foot care, instead of a complex set of behaviors, significantly improves the probability of achieving goals. Thirdly, many environmental and external factors affect patients' adherence to self-care behaviors, which are constantly changing. Therefore, it should not be expected that simply providing a temporary and brief training program would solve the problems permanently and completely. Finally, the evaluation of the results in the present study was conducted 3 months after the training, making it impossible to make a correct judgment about the stability of the educational intervention. To make a more decisive decision about the stability of the results of the educational intervention, several follow-ups with time intervals of 6 months and one year will be necessary.

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Data avaliablity statement

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

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No conflicts of interest are declared by the authors.

Authors' contributions

IMZ: Conceptualization, Methodology and data analysis and FSB data collection and manuscript writing.

All Authors revised the manuscript and gave their contribution to improve the paper. All authors read and approved the final manuscript.

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NON COMMUNICABLE DISEASES

Barriers to Breast Cancer Screening Tools in a Cohort of Urban Indian Women

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Keywords

Breast Neoplasms • Mass Screening • Early Detection of Cancer • Barriers

Summary

Introduction. *Breast cancer has the highest incidence and mortality rate in India. Early detection of Breast cancer has better survival chances and reduces treatment costs. Breast cancer screening involves Breast Self-Examination (BSE), Clinical Breast Examination (CBE), and Mammography. The highest burden of breast cancer has been observed in metropolitan cities. So it becomes crucial to assess breast cancer awareness and screening practices among urban women. Moreover, currently, there is a significant gap in the literature concerning the barriers that affect screening practices amongst Indian women.*
Methods. *We conducted a survey-based, cross-sectional study on urban Indian women living in Uttar Pradesh. Women for this study were selected based on predefined inclusion and exclusion criteria. The data were collected using a self-administered questionnaire which included the socio-demographic variables (address, age, occupation, education level, marital status) of the participants and cancer and cancer screening-related questions.*
Results. *612 urban women in Uttar Pradesh, India participated in our study. Most were married (96%) and unemployed (59%). Approximately 76% had received education at the high school level or higher, while only 19% had health insurance. The participants' ages ranged from 30 to 70 years, with a mean age of 41 years ± 8.25 years).*
Conclusions. *Our study revealed high breast cancer awareness among participants but disparities in screening awareness based on age, marital status, insurance, and education. Most women have a positive attitude towards breast cancer screening, recognizing its importance for early detection. This attitude can drive participation if barriers are addressed, including knowledge gaps, symptom ignorance, shyness, financial constraints, and a lack of female doctors.*

Introduction

Cancer remains the second leading cause of death worldwide, with the global cancer burden projected to reach 35 million cases by 2050, according to the latest estimates from the Global Cancer Observatory (GLOBOCAN) 2023 [1]. Among all cancers, breast cancer is the most commonly diagnosed malignancy and remains the leading cause of cancer-related deaths among women [2]. In India, breast cancer incidence has been steadily rising, now accounting for approximately 14.8% of all cancer cases and 12.3% of cancer-related deaths among women, as per the Indian Council of Medical Research (ICMR) report 2023 [2, 3]. Given the absence of well-defined modifiable risk factors, early detection, accurate diagnosis, and timely treatment initiation are crucial for improving survival rates [4].

To facilitate early detection, breast cancer screening primarily relies on mammography, which is the only internationally accepted modality for breast cancer screening. Mammography, an X-ray imaging technique, is considered the gold standard, with evidence demonstrating a 20-30% reduction in mortality among women aged 50 years and older who undergo regular screening [5, 6]. However, in resource-limited settings such as India, where access to mammography may be restricted, breast self-examination (BSE) and clinical breast examination (CBE) serve as adjunctive methods to enhance early detection efforts. BSE, a self-performed technique, and CBE, conducted by trained healthcare professionals, help improve breast cancer awareness and may facilitate earlier diagnosis, particularly in low-resource environments where mammography is not widely available [7].

In India, despite the integration of breast cancer screening into the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDC), participation remains alarmingly low [8]. More than 70% of breast cancer cases in India are diagnosed at an advanced stage, significantly reducing the chances of successful treatment [9]. Findings from the National Family Health Survey-5 (NFHS-5) further highlight this issue, revealing that fewer than 0.5% of women aged 30-49 have undergone a CBE [10, 11]. This lack of widespread screening underscores the urgent need to identify and address barriers to participation.

Multiple factors influence breast cancer screening rates, broadly categorized into personal, economic, and healthcare service-related barriers. Socioeconomic

status, education level, and family history of breast cancer play a critical role in determining whether a woman undergoes screening [12]. In many developing countries, the high mortality associated with breast cancer is largely attributed to inadequate screening programs, limited awareness, and restricted access to healthcare services [13].

Among these barriers, lack of awareness and education stands out as a key reason for poor screening uptake in India [14]. Addressing these challenges is essential for improving screening participation and enhancing early detection efforts. However, there remains a significant gap in the existing literature regarding the specific factors that influence screening behaviours among Indian women. To bridge this gap, this study aims to identify the barriers to breast cancer screening among urban women in India and explore the underlying reasons for these obstacles. By examining factors such as awareness, socioeconomic constraints, and demographic profile, this research seeks to provide insights that can inform targeted interventions to improve screening uptake and early detection efforts.

Methods

This survey-based, cross-sectional study was conducted on urban Indian women residing in Uttar Pradesh. Indian women living in urban areas who had no complaints of breast-related diseases at any stage of their lives were included in the study. Women who did not complete at least 70% of the questionnaire were excluded from the study. Participants were recruited using a population-based sampling strategy from healthcare facilities. The study population included women attendants accompanying patients to the healthcare facilities. Trained survey administrators informed potential participants about the study objectives and obtained written informed consent before administering the questionnaire.

Data was collected by administering a comprehensive self-designed, pre-validated, structured questionnaire through both offline and online methods. The questionnaire was validated by a pilot study on a small sample (n = 30) to assess clarity and reliability. Necessary modifications were made based on participant feedback before full-scale data collection. The questionnaire was also made available in the local language for the participants to choose from. It included socio-demographic variables (address, age, occupation, education level, marital status) of the participants, along with cancer screening-related questions (about Breast Self-Examination, Clinical Breast Examination, and Mammography). Women who had limited access to healthcare settings may have been underrepresented, which could have influenced the findings. After data collection, the data obtained were analyzed with the help of IBM SPSS (Statistical Package for the Social Sciences) Software Version 24 (USine).

Results

This cross-sectional study was conducted on 612 women. Among them, the majority were married (95.8%, n = 586) and unemployed (59.3%, n = 363). A significant proportion (76.3%, n = 467) had received education at the high school level or higher, and only 18.5% (n = 113) possessed health insurance. The mean age of participants was 41 ± 8.25 years, with the majority (49%, n = 300) in the 31-40 years age group.

A high proportion of women (94.3%, n = 577) were aware of breast cancer, but awareness of screening methods was lower (74.7%, n = 457). Knowledge of breast self-examination (BSE) was reported by 67.6% (n = 414), clinical breast examination (CBE) by 71.6% (n = 438), and mammography by 56.5% (n = 346). Awareness of breast cancer was significantly associated with age ($p = 0.043$, $r = -0.056$) and education level ($p = 0.002$, $r = -0.094$), emphasizing the role of educational interventions in enhancing knowledge and promoting early detection strategies. Awareness of breast cancer screening was influenced by age ($p = 0.034$, $r = -0.023$), marital status ($p = 0.037$, $r = 0.085$), insurance status ($p = 0.003$, $r = 0.122$), and education level ($p < 0.001$, $r = -0.175$), highlighting the need for targeted public health campaigns to reach underserved populations (Tab. I, Figs. 1, 2).

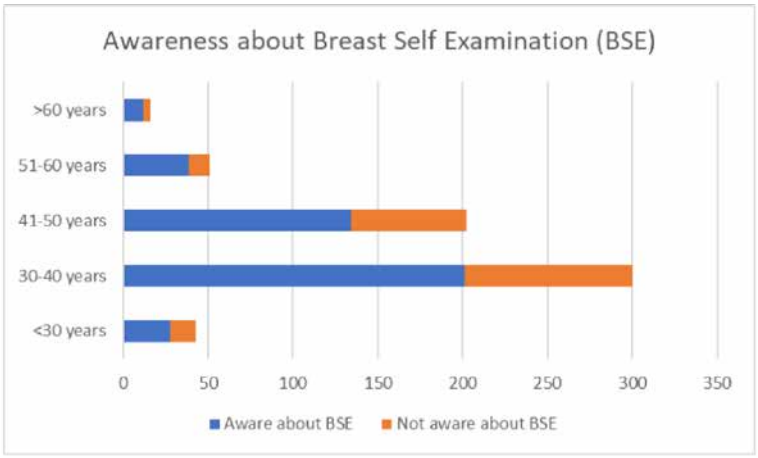
Despite the relatively high awareness of BSE (67.6%, n = 414), only 37.7% (n = 231) knew the correct technique, and even fewer (29.7%, n = 182) practiced it regularly. These screening behaviours and their demographic associations are detailed in Table II. Barriers to BSE included lack of knowledge (35%, n = 214) and the absence of symptoms (22.5%, n = 138). Of the women who performed regular BSE, 5.7% (n = 35) detected abnormalities, and only 4.7% (n = 29) sought medical consultation, indicating a gap between awareness and action that could delay the detection of potential malignancies (Tab. III). BSE awareness was influenced by occupation ($p = 0.020$, $r = 0.078$), insurance status ($p = 0.003$, $r = 0.122$), and education level ($p<0.000$, $r = -0.238$), while its practice was associated with marital status ($p = 0.021$, $r = 0.093$). These findings underscore the need for structured training programs to improve self-screening practices, which could enhance early cancer detection rates and reduce mortality.

Although 71.6% (n = 438) of women had knowledge of CBE and 65.2% (n = 399) believed in its efficacy, only 19.4% (n = 119) had ever undergone CBE, with a vast majority (80.6%, n = 493) never having been examined by a healthcare provider. This significant disparity between knowledge and practice suggests a lack of access or perceived necessity, which may contribute to late-stage breast cancer diagnoses. Preference for female healthcare workers (64.7%, n = 396) and specialists like breast surgeons (52.3%, n = 320) and gynecologists (30.9%, n = 189) suggests that increasing the availability of female providers could improve screening rates (Tab. IV). Awareness of CBE was significantly influenced by age ($p = 0.000$, $r = 0.104$), while the decision to undergo

Tab. I. Awareness about Breast Cancer Screening Techniques among urban Indian women.

Demographics	Awareness about BSE		P-value	Awareness about CBE		P-value	Awareness about Mammography		P-value
	Yes (n)	No (n)		Yes (n)	No (n)		Yes (n)	No (n)	
Age Group									
< 30 (43)	28	15	0.636	34	9	**<0.001**	31	12	**0.011**
30-40 (300)	201	99		229	71		162	138	
41-50 (202)	134	68		126	76		105	97	
51-60 (51)	39	12		42	9		37	14	
> 60 (16)	12	4		7	9		11	5	
Marital status									
Single (26)	22	4	0.084	15	11	0.121	13	13	0.492
Married (586)	392	194		423	163		333	253	
Occupation									
Employed (241)	176	65	**0.020**	169	72	0.794	144	97	0.419
Unemployed (363)	231	132		263	100		198	165	
Student (8)	7	1		6	2		4	4	
Insurance									
Yes (113)	90	23	**0.003**	83	30	0.646	71	42	0.135
No (499)	324	175		355	144		275	224	
Education Level									
Under class 10 (133)	71	62	**<0.001**	100	33	0.245	80	53	0.507
Class 10 (57)	26	31		36	21		26	31	
Class 12 (70)	49	21		53	17		38	32	
Undergraduate (158)	111	47		117	41		96	62	
Postgraduate (170)	137	33		112	58		94	76	
PHD (12)	11	1		10	2		6	6	
Illiterate (12)	9	3		10	2		6	6	

Fig. 1. Bar chart representing the awareness about breast self-examination (BSE) among various age groups.

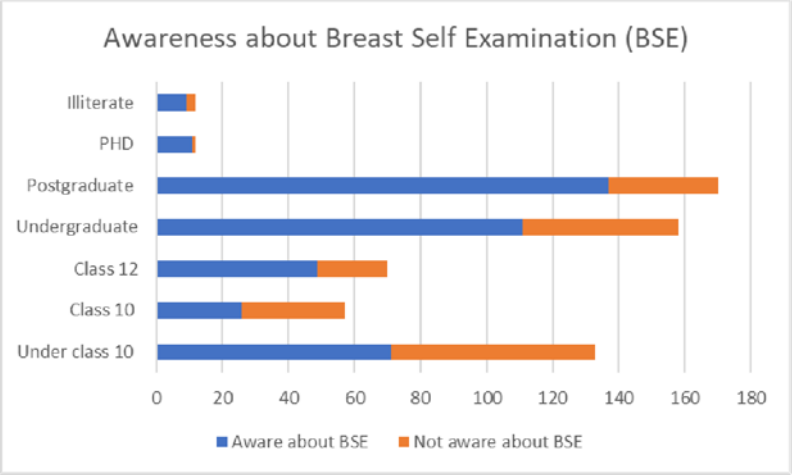


CBE was affected by occupation (p = 0.003, r = 0.127) and health insurance (p = 0.017, r = 0.096), reinforcing the need for affordable and accessible screening programs in both urban and rural settings (Tab. I).

Approximately 56.5% (n = 346) of the women were aware of mammography, with 52.5% (n = 321) believing it to be a valuable tool for early breast cancer detection. However, 89.1% (n = 545) women had never undergone screening mammography, and only 20 (3.3%) women reported recent screenings. This low utilization rate suggests significant barriers to access, affordability, or awareness that could contribute to delayed cancer diagnoses and poorer prognoses. Awareness of mammography (p = 0.011, r = -0.025) and its practice (p = 0.003, r = -0.069) were affected by age, with no significant association with marital status, occupation, insurance, or education level (Tab. I). These findings emphasize the need for policies promoting routine mammography screening, particularly for high-risk groups, to improve early detection and survival rates.

A significant portion of the women (73%, n = 446) felt that breast cancer screening was essential for early detection, while 47% (n = 290) believed it should be done only when necessary. A small percentage cited cultural

Fig. 2. Bar chart representing the awareness about breast self-examination (BSE) among various education groups.



Tab. II. Breast Cancer Screening practices among urban Indian women.

	BSE Practice		P-value	Underwent CBE		P-value	Underwent Mammography		P-value
	Yes (n)	No (n)		Yes (n)	No (n)		Yes (n)	No (n)	
Age Group									
< 30 (43)	9	34	0.168	6	37	0.850	5	38	**0.003**
30-40 (300)	86	214		58	242		28	272	
41-50 (202)	60	142		40	162		19	183	
51-60 (51)	22	29		12	39		14	37	
> 60 (16)	5	11		3	13		1	15	
Marital status									
Single (26)	13	13	**0.021**	4	22	0.593	1	25	0.344
Married (586)	169	417		115	471		66	520	
Occupation									
Employed (241)	78	163	0.413	63	178	**0.003**	33	208	0.158
Unemployed (363)	101	262		54	309		33	330	
Student (8)	3	5		2	6		1	7	
Insurance									
Yes (113)	41	72	0.110	31	82	**0.017**	14	99	0.617
No (499)	141	358		88	411		53	446	
Education Level									
Under class 10 (133)	27	106	0.056	17	116	0.078	13	120	0.877
Class 10 (57)	16	41		9	48		9	48	
Class 12 (70)	17	53		18	52		9	61	
Undergraduate (158)	50	108		32	126		16	142	
Postgraduate (170)	63	107		34	136		17	153	
PHD (12)	4	8		4	8		2	10	
Illiterate (12)	5	7		5	7		1	11	

(5%) or religious (3%) reasons against screening. Most women (83%, n = 510) were comfortable discussing breast cancer with a physician, while 88% (n = 539) did not feel embarrassed discussing it in society.

Inadequate knowledge about breast cancer and screening was perceived as the most significant barrier to clinical breast examination for 67% (n = 410) of women and mammography for 54.9% (n = 336). Additionally, ignorance of cancer-related symptoms was perceived as a barrier for both CBE and mammography for 67.3% (n = 412) and 54.6% (n = 334) of women, respectively. Shyness, hesitation, or embarrassment were perceived as barriers for 55.9% (n = 342) in CBE and 46.4% (n = 284) in mammography. Financial constraints were reported by 48.5% (n = 297) and 44.1% (n = 270) as barriers to CBE and mammography, respectively. Lack of female doctors in healthcare facilities was noted as a barrier by 41.8% (n = 256) for CBE and 37.3% (n = 228) for mammography.

It was determined that seeking healthcare professionals support was influenced by several factors, including fatalism (p = 0.021), financial constraints experienced by women (p = 0.008), time constraints (p = 0.007), transportation issues (p = 0.035), apprehension about

Tab. III. Breast Self-Examination (BSE) practices among urban Indian women.

Questions	Participants Response	
	n	%
Do you know how to perform BSE?		
Yes	231	37.7
No	183	29.9
Haven't heard about BSE.	198	32.4
How often do you perform BSE?		
Weekly	32	5.2
Monthly	41	6.7
Occasionally	90	14.7
Rarely	19	3.1
If you have been practising BSE, have you ever discovered any abnormality in your breast?		
Yes	35	5.7
No	147	24
If the answer to the question above is yes, what did you do?		
Consulted a doctor	29	4.7
Did nothing	6	1.0
If you've heard about BSE and still do not perform BSE, What is the reason?		
I don't know how to perform BSE	214	35.0
I don't have any symptoms of breast cancer	138	22.5
I believe that I can never have breast cancer	15	2.5
I am scared of being diagnosed with breast cancer	25	4.1
Doing BSE makes me worry about breast cancer	22	3.6
Doing BSE is embarrassing to me	13	2.1
I don't have enough privacy to do BSE	15	2.5
I don't believe in the efficacy of this test	12	2.0
I don't think I should touch my body like that again & again	22	3.6
BSE takes too much time.	17	2.8
BSE is unpleasant/ painful	10	1.6
I don't think BSE is important	12	2.0

Tab. IV. Clinical Breast Examination (CBE) practices among urban Indian women.

Questions	Participants Response	
	n	%
What centre would you like to visit for CBE?		
PHC	32	5.2
CHC	27	4.4
Any Government Hospital	318	**52**
Any Private Hospital	100	16.3
Anywhere	135	22.1
Gender preference of healthcare provider while undergoing CBE:		
Male	11	1.8
Female	396	**64.7**
Anyone	205	33.5
Which doctor would you prefer for CBE?		
General Physician	19	3.1
Breast Surgeon	320	**52.3**
Gynecologist	189	30.9
Anyone	84	13.7
Are you comfortable discussing breast cancer with a physician?		
Yes	510	**83.3**
No	102	16.7
Do you feel embarrassed talking about breast cancer in society?		
Yes	73	11.9
No	539	**88.1**
How do you feel about undergoing breast cancer screening?		
It is better for early detection	446	72.9
It should be done only when the need arises	290	47.4
It is culturally unacceptable	29	4.7
I have religious issues in doing so	17	2.8

diagnosis (p = 0.002), and fear of pain (p = 0.002) (Tab. V). Similarly, the study revealed that the utilization of screening mammography among women was influenced by factors such as time constraints (p = 0.025), anxiety related to potential diagnosis (p = 0.030), and concerns about the discomfort associated with the procedure (p = 0.004) (Tab. V). To improve participation rates, healthcare systems should focus on reducing wait times, ensuring patient comfort, and addressing anxiety through counseling and educational programs.

Discussion

The study found that the majority of respondents (94%) in our cohort exhibited familiarity with the concept of breast cancer, with approximately 75% of these women having awareness of breast cancer screening. Our findings deviate from those reported by Oswal et al. [15], wherein breast cancer awareness was documented at 50%, and awareness of breast cancer screening stood at 34%. Our study revealed that 68% of women were acquainted with breast self-examination (BSE), 72% were conversant with clinical breast examination (CBE), and 57% were informed about mammography. These results contrast with those obtained in a systematic review conducted by Taneja et al. [16], which documented knowledge levels of 41% for BSE, 51% for CBE, and 46% for mammography. Furthermore, the same review reported that 27% of women practiced regular BSE, a figure that closely mirrors our finding of 30% of participants regularly engaging in BSE. The higher awareness observed among our participants may be attributed to our study's exclusive focus on urban women, thereby excluding rural populations. These findings align with other studies from southern and western regions of India, where urban populations demonstrated higher awareness than their rural counterparts [19, 20]. However, the disparity in awareness levels across different regions suggests the need for region-specific strategies to improve breast cancer education.

A noteworthy revelation was that 35% of women

Tab. V. Barriers to Breast Cancer Screening experienced by urban Indian women.

Potential Barriers to Breast Cancer Screening	Underwent CBE			P-Value	Underwent Mammography			P-Value
	Yes (n)	No (n)	Total (n)		Yes (n)	No (n)	Total (n)	
Culture/traditions of the family	39	134	173	0.257	17	95	112	0.131
Ignorance of symptoms related to cancer	83	329	412	0.587	41	293	334	0.298
Fatalism	32	86	118	**0.021**	14	99	113	0.617
Traditional healers' (Ayurveda, Unani, Homeopathy, etc.) consultation	43	140	183	0.118	16	128	144	1.000
Shyness, Hesitant or Embarrassment / Reluctance to discuss such issues	75	267	342	0.100	39	245	284	0.051
No screening facilities in the area	48	165	213	0.165	22	169	191	0.781
No female doctor available	58	198	256	0.098	32	196	228	0.062
Inadequate knowledge regarding breast cancer & screening	82	328	410	0.665	38	298	336	0.796
Financial Problems	71	226	297	**0.008**	35	235	270	0.192
Lack of time or long waiting time for appointments	55	161	216	**0.007**	29	161	190	**0.025**
Geographic & Transportation Problem	39	115	154	**0.035**	20	129	149	0.291
Conservative society	30	112	142	0.628	10	95	105	0.732
Fear of diagnosis	50	134	184	**0.002**	22	114	136	**0.030**
Fear of pain	48	128	176	**0.002**	25	116	141	**0.004**
Negative past experiences (e.g. inappropriate services, bad behaviour, etc)	39	149	188	0.658	11	117	128	0.349
Language barrier	22	82	104	0.683	13	83	96	0.477

refrained from its practice due to a lack of proficiency in the technique. This underscores the need to develop breast cancer awareness initiatives with an intensified focus on educating individuals about BSE. This emphasis is justified by the unique nature of breast cancer, characterized by its occurrence in an externally observable organ, allowing for early-stage detection and treatment. Given the low-resource setting in many areas, community health workers could play a crucial role in BSE education through cost-effective, community-based training programs. Additionally, integrating BSE instruction into routine health check-ups or maternal health programs could ensure wider outreach.

Regrettably, our study unveiled that 81% of women admitted to never having undergone breast examination by a healthcare professional. Barriers such as shyness, hesitation, or embarrassment were cited by 56% in the context of CBE and 46% regarding mammography. Financial constraints constituted an impediment for 49% and 44% concerning CBE and mammography, respectively. Additionally, the absence of female healthcare providers within healthcare facilities was perceived as a barrier by 42% for CBE and 37% for mammography. Eliminating these hindrances could potentially amplify women's participation in CBE, as evidenced by the preference for government hospitals (52%) over private institutions (16%) for CBE. Furthermore, a substantial majority (65%) of women expressed a preference for female healthcare providers when undergoing CBE. To address these barriers in resource-limited settings, strategies such as subsidized screening programs, mobile screening units, and task-sharing with trained nurses could be explored. Ensuring the availability of female healthcare providers, particularly in public hospitals, could further encourage participation in CBE and mammography screening.

Our findings revealed that a striking 89% of women had never undergone screening mammography. This observation can be attributed to the economic constraints associated with mammography, rendering it less amenable to routine screening in a developing nation such as India [17]. Previous studies from similar developing countries, including Bangladesh and Pakistan, have also highlighted cost as a major impediment to mammography utilization [18]. This underscores the necessity of advocating for government-supported screening programs and insurance schemes that cover breast cancer screening to improve accessibility.

Interestingly, despite the participants' relatively high educational levels, 67% and 55% of respondents perceived "inadequate knowledge about breast cancer and screening" as the primary barrier to CBE and mammography, respectively. This finding corroborates

previous research by Aghadash et al. [19]. Other barriers, as perceived by the women in our study, encompassed ignorance of cancer-related symptoms, shyness, hesitation or embarrassment, and financial constraints.

Our study found an encouragingly high level of awareness about breast cancer among participants. However, disparities exist in awareness of breast cancer screening methods, with variations related to age, marital status, insurance, and education level. This suggests the need for targeted educational interventions to improve awareness among specific subgroups. Although awareness of BSE is relatively high, a concerning proportion of women who are aware of BSE do not practice it regularly due to a lack of knowledge about the proper technique and the absence of symptoms. These findings highlight the importance of not only raising awareness but also providing practical training and education on how to perform BSE correctly.

Similarly, awareness of CBE is high, but its utilization is low, with most women reporting never having undergone a clinical breast examination by a healthcare provider. This gap between awareness and utilization could be attributed to various factors, including preferences for specific healthcare facilities and providers. Efforts to promote mammography should focus on addressing these personal barriers.

Several barriers to breast cancer screening were identified, including inadequate knowledge, ignorance of symptoms, shyness, financial constraints, and the lack of female doctors in healthcare facilities. These findings underscore the multifaceted nature of the challenges that need to be addressed through targeted interventions such as educational campaigns, increased availability of female healthcare providers, and addressing financial barriers. Future research should explore the effectiveness of community-based breast cancer screening programs in low-resource settings, evaluate digital health interventions for awareness campaigns, and examine the impact of policy changes on screening participation rates. Additionally, longitudinal studies tracking women's participation in screening programs over time could provide deeper insights into behavioural trends and intervention efficacy.

Conclusion

Our research highlights both encouraging trends, such as high awareness and positive attitudes toward breast cancer screening, and concerning gaps, including low utilization rates and significant barriers. These findings provide valuable insights for policymakers to develop targeted strategies to improve screening rates and reduce the disease burden. Future research should explore context-specific interventions, such as mobile screening units, financial assistance models, and community outreach programs, particularly in rural areas. Increasing the availability of female healthcare providers and implementing educational campaigns for specific subgroups can further enhance screening uptake. Comparative studies between urban and rural populations will help identify tailored solutions to address healthcare access, cultural perceptions, and economic constraints.

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Ethical approval

The study was conducted only after approval by the Institutional Ethics Committee (IEC) of King George's Medical University, Lucknow (Reg No: XI-PGTSC-II B MBBS-S/P9), vide Letter: 869/Ethics/2022, dated: 04/08/2022. The details and data collected from the subjects were blinded, and confidentiality was maintained.

Conflict of interest statement

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Authors' contributions

The author contributions are as followed: VS: Conceptualization, Methodology, Investigation, Data curation, Writing- Original Draft. MS: Formal analysis, Writing-Review & Editing, Visualization, Literature review. GN: Supervision, Validation, Writing-Review & Editing. PS: Project administration, Resources, Supervision

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History of medicine and ethics

Investigating the Theoretical Possibility of Dengue Fever in Ancient Egypt

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Keywords

Ancient Egypt • Dengue; fever • History of medicine • Infectious diseases • Mosquito • Palaeopathology

Summary

Dengue fever, a mosquito-borne viral disease primarily transmitted by Aedes aegypti, has become a growing global health concern, with dramatic increases in incidence in recent years. Although no direct evidence of dengue exists from ancient Egypt, this study investigates the theoretical possibility of its presence in that historical context. The approach integrates palaeoclimatic data, modern entomological and vector ecology studies, molecular clock analyses, and the interpretation of ancient Egyptian medical papyri. Special attention is given to the term temyt, described in association with dermatological and neurological symptoms in children and linked to the demon nesyt, as reinterpreted by scholars such as Bruno Halioua and Pascal Hannequin. These sources are critically re-evaluated alongside modern clinical symptomatology of dengue. Findings suggest that environmental and climatic conditions in ancient Egypt – particularly in regions like the Fayum– could have supported Aedes populations, and that certain disease descriptions may reflect empirical observations of vector-borne illnesses. While the evidence remains circumstantial and speculative, it opens new interpretative avenues regarding ancient Egyptian understandings of febrile, eruptive childhood diseases. The study concludes that dengue or dengue-like syndromes cannot be ruled out and that future interdisciplinary research, including palaeogenetic and archaeoviral approaches, may help clarify the presence of arboviral diseases in antiquity.

Introduction

The history of the scientific name of the yellow fever mosquito, the vector of the yellow fever virus, dates back to the late 18th century. In his 1757 work *Iter Palæstinum***,** Frederic Hasselquist described a mosquito, which he named *Culex aegypti***,** which was responsible for a very serious disease, which was very common in Egypt [1]. Linnaeus edited the writings of Hasselquist and included this mosquito in his nomenclature [2]. When the vector of the unknown yellow fever agent was identified in Cuba in the late 19th century, it was named *Stegomyia fasciata* [3]. The classifications multiplied, as different mosquitoes were identified and a heated debate about the nomenclature began until *Stegomyia* was relegated to the subgeneric rank of *Aedes* [4]. The term Aedes derives from the Ancient Greek adjective ἀηδής (aēdḗs, "unpleasant, odious"), ἀ- (a-, "un-") + ἡδύς (hēdús, "sweet, pleasant") [5]. Closely connected with this vector **is** dengue fever (DENV), which is a rapidly spreading arboviral disease, with recent years witnessing unprecedented outbreaks. In 2024, over 12.4 million cases were reported globally, doubling the 6.5 million cases from 2023 [6]. This surge is attributed to factors such as climate change, urbanisation, and increased human mobility [7]. The World Health Organization (WHO) has launched a global strategic plan to combat the rise of dengue and other Aedes-borne diseases, emphasising the need for coordinated surveillance and vector control efforts [8]. With particular reference to Egypt, dengue fever has re-emerged as a public health concern. After the eradication of *Aedes aegypti* in 1963 [9], the vector has been detected again in various regions, including the Nile Valley and Red Sea coast [9]. In 2023, Germany reported 36 dengue cases among travellers returning from Egypt, particularly from the Red Sea resort areas [10]. Furthermore, in May 2024, three Italian travellers were diagnosed with dengue after visiting Sharm El Sheikh, marking the first reported cases from this popular tourist destination [11]. Given the current epidemiological landscape, this study investigates the theoretical possibility of dengue fever's presence in ancient Egypt. By examining historical medical descriptions, environmental conditions, and vector ecology, we aim to assess whether ancient Egyptians could have encountered a disease analogous to modern dengue.

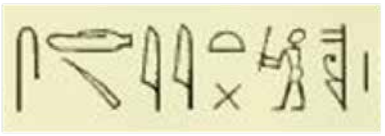
Problematising Halioua's retrospective diagnosis of measles in Ancient Egypt

Ancient Egyptian medical papyri provide insights into the civilisation's understanding of diseases. Bruno Halioua, in his work *La médecine au temps des pharaons*, discusses the interpretative challenges of aligning ancient disease descriptions with modern diagnostics [12]. For instance, a pathogenic substance described in the Hearst papyrus (n. 168, 10-12), known as *temyt, is said to be treated by means of therapies aimed at expelling it, such as charcoal, liquid residue, wheat starch, sea salt, castor bean, dates, pyrethrum seeds, honey [12].*
The following original passage is reported from Grapow's edition of the papyrus [13], as detailed in the following image (Fig. 1).

Fig. 1. The tmjt-*Krankheit*, from H. Grapow, 1958

Halioua considers this *temyt* to be "a childhood disease by definition: a violent skin eruption that the Egyptians attributed to the action of a mysterious substance (*temyt*) that had to be fought", which is based on Pascal Hannequin's view that "the *temyt* substance manifests itself through cutaneous signs and affects children (it is not found in passages concerning adults)" - (authors' translation of both passages) [14]. Hannequin's considerations are based on the London Papyrus 6 (3, 1-5) where a disease affecting Horus' skin is hinted at [14], although – it should be remarked – the description appears to be somewhat fragmentary and vague to make a clear-cut retrospective diagnosis. Halioua, then, also explores the *temyt pathogenic substance/disease in the* Berlin Papyrus (n. 3027, 1, 4-9) [12].
The following passage (Fig. 2) is from the Erman 1901 edition [15].

Fig. 3. The word *sḏy.t qs* in hieroglyphic script.

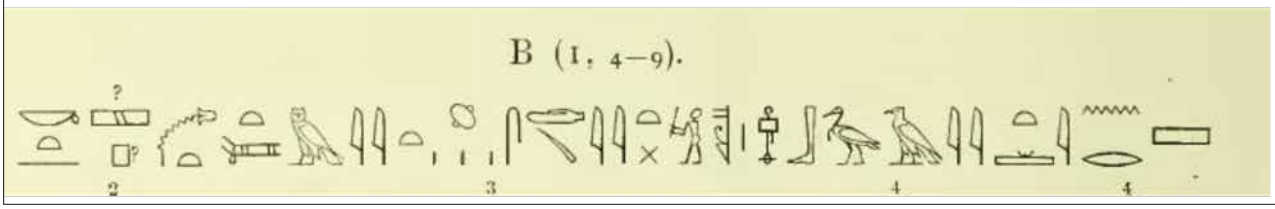


Worthy of note, in this passage, is the reference to temyt, followed by the attribute *sḏy.t qs* (Fig. 3), which literally means "she who belongs to the bone-breaking", hence "the bone-breaker" – *Knochenbrecherin* in the German translation by Adolf Erman (1854-1937) [15].
Subsequently, Halioua draws on the mentioned London Papyrus (n. 6, 3, 1-15) and Hannequin's work to connect *temyt* with the disease-causing demon *nesyt* and follows the latter scholar's 2001 formulation:

> *Certains auteurs ont identifié le démon-nesyt à des troubles neurologiques voire même à l'épilepsie. Nous sommes donc devant une maladie infantile présentant des signes dermatologiques et parfois neurologiques, semblant relativement grave (noter qu'aucun des textes ne pronostiquent une éventuelle guérison). Ces textes pourraient donc se rapporter à la rougeole, responsable encore maintenant de nombreux décès d'enfants dans les pays en voie de développement* [14].
>
> ["Some authors have identified demon-*nesyt* with neurological disorders and even epilepsy. We are therefore dealing with an infantile disease with dermatological and sometimes neurological signs, which appears to be relatively serious (note that none of the texts prognosticate a possible cure). These texts could therefore relate to measles, which is still responsible for many child deaths in developing countries" – authors' translation]

Hence, according to Hannequin and Halioua, ultimately *temyt* could be a reference to measles [12, 14]. The basis for this interpretation is to be ascribed to: a. the paediatric patient category described; b. the cutaneous manifestations Halioua describes without a direct reference to a specific passage; c. the *temyt-nesyt*-neurological connection.
While the two scholars' morbillous interpretation is certainly a plausible hypothesis worth considering, it should be underlined that measles is widely believed to have emerged as a distinct human disease during the early Middle Ages, likely evolving from the rinderpest

Fig. 2. Hieroglyphic passage from Erman, 1901.



virus in animal populations before adapting to humans. Molecular clock analyses estimate this zoonotic jump occurred around the 6th century AD, coinciding with the rise of large urban centres that could sustain the continuous transmission required for measles' survival [16]. The first clear clinical description is attributed to the Persian physician al-Razi (Rhazes, ca. AD 864/865–AD 925/935) in the 9th century, who differentiated measles from smallpox in his treatise *Kitab al-Jadari wa al-Hasbah* (*i.e., The Book of Smallpox and Measles*), highlighting the disease's fever, rash, and respiratory symptoms. This supports the view that measles, as we know it today, was first recognised and described in the Islamic Golden Age [16]. However, some scholars argue for its presence in antiquity [17]. Classical accounts occasionally mention childhood diseases characterised by fever and eruptive symptoms. Historian Kyle Harper notes that while retrospective diagnosis is inherently speculative, certain descriptions in Greco-Roman medical and historical texts suggest the circulation of illnesses compatible with measles. He acknowledges the ambiguity of such sources but argues that the demographic and urban conditions of the Roman Empire may have allowed for sustained transmission of measles-like pathogens before the Middle Ages [17]. Thus, while the prevailing consensus favors a Mediaeval emergence, the hypothesis of earlier outbreaks remains plausible.

Returning to Halioua's analysis, the reference to measles in a paediatric context may appear to support identifying *temyt* as that infectious disease. Nonetheless, although he mentions the bone-breaking property of *temyt*, Halioua does not elaborate further on it [12], nor does Hannequin [14].

Despite the symbolic language, this symptom could suggest an alternative interpretation: dengue. Classical dengue fever typically presents with sudden high fever, rash, severe headache, retro-orbital pain, muscle and joint pain (which earned it the nickname "breakbone fever"), and general malaise [18]. In children, dengue may also cause irritability, skin manifestations, and in severe cases, neurological symptoms like seizures or altered consciousness, which are commonly associated with dengue shock syndrome or dengue encephalitis [19]. Moreover, the reference to bone-related pain or disease in ancient texts – while metaphorical– may correspond to the deep musculoskeletal pain and systemic inflammation typical of dengue. The ancient therapeutic use of castor oil and pyrethrum seeds, both known for their insecticidal or anti-inflammatory properties, suggests a symptomatic treatment of the illness, even if its aetiology remained unexplained.

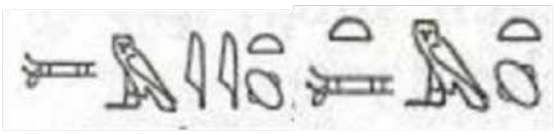
As far as neurological manifestations of dengue in children, many have been reported such as encephalopathy, encephalitis, seizures, motor complications, sleep disorders, etc. [20], hence neurological complications or sequelae would not be exclusively observable in measles although one can concede to Hannequin and Halioua that measles has a higher rate of severe neurological complications such as measles encephalitis (1 in 1,000 cases) and SSPE (1 in 10,000–25,000), which is often fatal [21].

Moreover, can one be sure that such vague cutaneous manifestations are really those of measles? Moreover, bone-cracking fever is not typical of measles and is, on the contrary, one of the main symptoms of the disease caused by *temyt*.

Temyt in the ancient Egyptian language

A compelling case study emerges from the interpretation of the above-mentioned term *temyt* (also spelt as *tmy.t*, *tmjt* or *temit*, Fig. 4, found in ancient Egyptian magical-medical texts and discussed by the late Egyptologist Rainer Hannig (1952-2022).

Fig. 4. Alternative forms of *temyt* in hieroglyphic script.



Listed tentatively among dermatological diseases, *temyt* is marked with an asterisk in Hannig's lexicon, indicating translation uncertainty [22]. Its characterisation as a demon-induced ailment (*von Dämonen bewirkt*) and the use of incantations aimed at banishing it from urban spaces back to swampy, rural regions suggests an environmental association that is particularly intriguing and goes in the direction of the previously described interpretation by Hannequin [12]. The described progression – from the swamp to the human population – evokes a pattern consistent with vector-borne disease transmission. Moreover, Erman's dating of the relevant spell to between the Hyksos period and the 19th and 20th Dynasties situates it within a timeframe consistent with the New Kingdom, when intensified agricultural activity and the colonisation of regions like the Fayum Oasis may have fostered ecological conditions conducive to mosquito proliferation. The association of the Fayum with stagnant waters and the emergence of malaria further strengthens the argument that *temyt* may reflect cultural memory or mythologisation of diseases spread via mosquitoes – possibly even dengue-like syndromes. The magical remedy's focus on repelling the disease to its environmental origin aligns conceptually with the vector control strategies of modern public health.

Discussion

Climatic and Ecological Conditions in Ancient Egypt

Ancient Egypt's climate was predominantly arid; however, the annual Nile floods created standing water bodies

ideal for mosquito breeding. During certain historical periods, particularly the Middle and New Kingdoms, palaeoclimatic studies indicate slightly more humid conditions in the Nile Valley due to increased monsoon influence [9]. These conditions could have supported the proliferation of mosquito species, including *Aedes aegypti*. Modern modelling studies predict that suitable habitats for *Aedes aegypti* are concentrated in the Nile Valley, Nile Delta, Fayoum Basin, Red Sea coast, and South Sinai. Projections under future climate change scenarios suggest an expansion of suitable habitats, particularly in the Nile Delta region, with a 61%-68% increase in suitable habitat area by 2050 [24]. These findings imply that similar ecological conditions could have existed in ancient times, facilitating the presence of dengue vectors.

Vector Ecology: Ancient and Modern Perspectives

Mosquitoes are frequently referenced in Egyptian texts and visual culture, and ancient remedies for insect repulsion are well-documented. While species-level identification is not possible from ancient remains, *Anopheles pharoensis* – a malaria vector – was long present in the region. The re-emergence of *Aedes aegypti* in modern Egypt due to climate change and urbanisation suggests that similar conditions could have supported the vector in ancient times [24]. Recent studies have confirmed the reappearance of *Aedes aegypti* in Egypt, particularly in Upper Egypt's governorates. In one study, 2,800 adult mosquitoes were captured near a dengue outbreak site, which provides evidence of the vector's re-establishment [24]. These findings underscore the importance of vector surveillance and control in mitigating dengue transmission.

Mosquitoes in ancient Egypt: Herodotus' account

Herodotus provides one of the earliest ethnographic observations of mosquito avoidance practices in Egypt. In *Histories* 2.95.1-3, he notes that Egyptians living in marshy areas employed various strategies to protect themselves from mosquitoes. Those residing in lower Egypt slept under fine fishing nets, not primarily to guard against bites, but to block the incessant noise of the insects:

> *Against the mosquitos that abound* [τοὺς κώνωπας ἀφθόνους ἐόντας]*, the following have been devised by them: those who dwell higher up than the marshy country are well served by the towers where they ascend to sleep, for the winds prevent the mosquitos from flying aloft; those living about the marshes have a different recourse, instead of the towers. Every one of them has a net* [ἀμφίβληστρον]*, with which he catches fish by day, and at night he sets it around the bed where he rests, then creeps under it and sleeps. If he sleeps wrapped in a garment or cloth, the mosquitos bite through it; but through the net they absolutely do not even venture* [25].

This passage reflects a culturally embedded response to a well-known environmental nuisance and may represent one of the earliest known uses of netting against insect vectors. Though Herodotus does not link mosquitoes to disease, his account offers valuable context for understanding ancient Egyptian awareness of, and adaptation to, mosquito presence along the Nile [26].

The antiquity of Dengue in light of molecular clocks

The evolutionary history of the dengue virus (DENV) reflects a long and intricate coevolution between the virus itself, its primary mosquito vector (*Aedes aegypti*), and primate hosts. It is widely believed that dengue originated as a sylvatic virus circulating among non-human primates in the forests of Southeast Asia or Africa, maintained through a transmission cycle involving forest-dwelling mosquitoes. Dengue belongs to the *Flavivirus* genus within the *Flaviviridae* family and exists in four closely related serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. Molecular clock studies suggest that the strains adapted to humans diverged from their sylvatic ancestors around 1,000 years ago [27, 28]. However, deeper divergence events – those separating sylvatic from endemic strains – may stretch back several thousand years, though these estimates become less precise with time. The virus likely made the leap to sustained human transmission when growing population centers and permanent settlements created the conditions for continuous cycles of mosquito-to-human transmission. *Aedes aegypti*, in particular, played a key role by adapting to human environments and breeding in water storage containers, thus becoming an efficient urban vector for the virus [27, 28]. Importantly, the estimate of approximately 1,000 years for the divergence of human-adapted dengue strains is based on genetic analyses of modern viral genomes, as ancient RNA virus sequences like those of DENV are exceptionally rare or virtually nonexistent due to their instability over time.

The convergence of symbolic medical descriptions, favorable microclimates, and potential vector habitats suggests the theoretical possibility of dengue fever in ancient Egypt. While the prevailing aridity might argue against it, the presence of Nile-related irrigation and water storage could have created microhabitats ideal for mosquito breeding, especially during the inundation season. Ancient descriptions of febrile illnesses accompanied by skin eruptions, the ritualistic use of fumigants, and the presence of remedies associated with dermatological or neurological symptoms may reflect an empirical recognition of vector-borne diseases, even if they lacked a precise etiology in modern terms. Moreover, the pairing of ailments with demonic forces such as *nesyt* and harmful substances like *temyt* suggests that diseases with both dermatological and neurological manifestations – such as severe or hemorrhagic forms of dengue – could have been conceptually assimilated into religious or magical paradigms. The symptomatology described – fever, rash, convulsions, irritability in children – parallels the profile, albeit

imprecisely, of dengue infections in modern pediatric cases. Furthermore, the therapeutic use of plant-derived compounds, such as pyrethrum seeds and castor oil (noted for anti-inflammatory and insecticidal properties), aligns intriguingly with modern approaches to symptom management and vector control. Whether through empirical observation or ritual practice, the ancient Egyptians appeared to respond to syndromes consistent with vector-borne illnesses.

Conclusion

While there is no direct evidence of dengue fever in ancient Egypt, its theoretical presence cannot be entirely dismissed. A multidisciplinary review reveals a set of circumstantial elements—favorable microclimates, the existence of potential mosquito vectors, suggestive disease descriptions in medical papyri, and environmental conditions compatible with dengue virus transmission. The recent epidemiological re-emergence of *Aedes aegypti* in modern Egypt reinforces the plausibility that the region, even in ancient times, may have supported mosquito populations capable of spreading dengue or dengue-like diseases. Bruno Halioua's interpretation of terms like *temyt* and *nesyt* in relation to childhood illness with neurological and dermatological symptoms opens the door to new speculative readings of ancient pathologies. While measles is the most common comparison for such symptoms, severe forms of dengue also present with overlapping clinical features, particularly in young children. Thus, a hypothetical case for dengue in ancient Egypt remains speculative but worthy of scholarly consideration. As modern Egypt confronts a re-emerging dengue threat in a warming climate, understanding its potential historical presence adds depth to both our epidemiological models and our appreciation of ancient medical knowledge. Future interdisciplinary research, including palaeogenetic studies of preserved tissues or further entomological analysis of ancient remains, could offer more definitive answers – as was the case for other ancient infectious diseases, such as leprosy, tuberculosis and tetanus, elucidated through palaeopathological approaches [29-32].

Data availability statement

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Informed consent statement

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Conflicts of interest statement

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

Authors' contributions

FMG, EV, MEH: conceived the study. FMG, EV, MEH, MM: designed the study. FMG, EV, MEH: drafted the manuscript. FMG, EV, MEH: original draft preparation. All authors performed a search of the literature, critically revised the manuscript and dealt with conceptualization, methodology, investigation, data curation, review and editing. All authors have read and approved the latest version of the paper for publication.

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History of medicine and ethics

Historical Perspectives on Scrofula: Competing Medical Discourses and Public Health Implications at the Turn of the 20th Century

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Kewords

Scrofula, medical history • Medical discourses • Contemporary public health

Summary

This article examines how scrofula was classified as a distinct disease in Danish medical history around the turn of the 20th century. Dr. Niemeyer, a naturopathic advocate, attributed scrofula to an unhealthy composition of bodily fluids, whereas Dr. Geill viewed it as a tuberculous condition and a precursor to pulmonary tuberculosis. While they differed on causation – particularly regarding heredity – they agreed on prevention strategies, emphasizing fresh air, skin care, nutrition, and physical activity to reduce contagion and improve children's resilience. Physicians advocated guiding children in dietary and hygienic practices to fortify their resistance against the tubercle bacillus.

The article highlights how naturopathic discourses were challenged by emerging claims that scrofula was an infectious disease. Expanding clinical assessments to include home hygiene and working conditions reflected broader shifts in societal health rationales. Public health measures required coordinated efforts between physicians and municipal authorities rather than being solely an individual responsibility.

Finally, this historical perspective is framed within a modern public health context, emphasizing the bio-psycho-social model of health and disease. It underscores the lasting relevance of interconnected health approaches, drawing parallels between past strategies against scrofula and contemporary public health efforts to address infectious and non-communicable diseases. Integrating historical insights into modern policy and practice can enhance health equity and prevention strategies.

Introduction

Tuberculosis serves as an excellent prism for understanding and discussing recent medical history, as its complex social, political, and medical dimensions reflect evolving perspectives and approaches within modern healthcare and public health policy [1-5]. In line with this, the study of scrofula has seen a resurgence in medical history research, with articles exploring its history in France [6], Italy [7-9], the UK [10], and Spain [11, 12]. The Spanish articles posit that scrofula has traversed three distinct stages in medical history: (a) the 'humoral' phase, originating in antiquity, wherein scrofula was perceived as a condition caused by an imbalance of the four bodily humors (blood, phlegm, yellow bile, and black bile); (b) the 'royal' phase, marked by the medieval belief, particularly in France and England, in the curative power of the royal touch [13-19]; and (c) the 'modern' phase, wherein scrofula was redefined as a distinct disease following the advent of bacteriology.

This article aims to explore how scrofula emerged as a defined medical entity in Denmark around the turn of the 20th century. Specifically, how was scrofula understood and classified as a disease in a Danish medical historical context? How was it delineated in such a way that contemporary physicians could recognize and diagnose it?

The analysis is based on two contemporary works that attributed specific manifestations to scrofula. Both books, authored by medical professionals, were published within a few years of each other, lending credibility to the source material. They are structured similarly, addressing the nature, causes, prevention, and treatment of the disease, allowing for a comparative analysis of commonalities and differences.

On one hand, German physician Paul Niemeyer (1832-1890) argued in his 1888 work *On Glandular Disease (Scrofula), Its Causes, Prevention, and Treatment* that the disease could be prevented and cured through a healthy lifestyle: "We can assume that Glandular Disease is fundamentally caused by child care practices that conflict with the principles of maintaining a healthy balance of bodily fluids, and generally against all healthy living habits" [20, p. 28]. Niemeyer's book was the fifth volume in a series for the *Medical Home Library* and aimed at a general audience. The same year, German naturopath Friedrich Eduard Bilz (1842-1922) published *Das neue Heilverfahren; Lehrbuch der naturgemäßen Heilweise und Gesundheitspflege*, which became a bestseller and

was translated into 12 languages, including a Danish edition titled *The New Naturopathic Method*. Both books emphasize achieving health through a healthy lifestyle, indicating a close connection between them. Conversely, Peter Christian Frederik Geill (1860–1938) posited in his 1890 work *Chest Diseases: The Origin, Prevention, and Cure of Pulmonary Tuberculosis with Special Regard to Domestic Conditions* that scrofula should be regarded as a precursor to pulmonary tuberculosis: "Signs of Scrofula [are] evidence that they already carry the seeds of [Tuberculosis] within them" [21, p. 49]. This statement directly links to the 1882 discovery by German physician Robert Koch of rod-shaped bacteria in the sputum of tuberculosis patients [22, p. 96].

This suggests that the naturopathic paradigm was challenged during this period by emerging views on scrofula as an infectious disease linked to tuberculosis. Physician Rolf Hertz (1868-1937) emphasized that "Tuberculosis is the dominant etiological factor in the development of Scrofula's varied symptoms" [23, p. 2]. The following sections will closely examine the source material to understand how Niemeyer and Geill perceived and presented scrofula in a Danish medical historical context.

The Manifestations of Scrofula

Niemeyer interpreted scrofula as the "result of an unhealthy composition of bodily fluids" [20, p. 7], and to assess the quality of these fluids, one had to consider their "total amount and nature." Physicians were "quite practiced in daily life at assessing" [20, p. 6] whether there was either too much fluid, leading to a bloated face, or too little, resulting in a thin and dry appearance. It was a common disease that physicians were accustomed to diagnosing. The face played a central role in Niemeyer's clinical assessment of whether a person was ill. If glands became inflamed in "glandularly weak, scrofulous children," swollen lymph vessels and nodes were often found on the "neck and nape," first appearing as "thick cords" and then as "large, tender knots," requiring surgical "incision to drain them" [20, p. 13].

Niemeyer described how scrofula could be pathologically characterized by lymph nodes forming "pea-sized, painless lumps that are movable under the skin and appear individually; later, they grow and can become as large as apples." These primarily appeared on the neck and under the jaw, but could also occur in other specific areas with clusters of lymph nodes, such as the armpit and groin [20, p. 38]. A distinctive symptom of scrofula was a thick-necked appearance, and the pig-like face (scrofa, Latin: sow) thus became the anchor of the clinical description. Over time, the affected lymph nodes formed "cheesy, matter-filled masses, which must be removed if accessible," potentially leaving a "cavernous sore, from which flows a sparse amount of matter mixed with cheesy clumps." These surgical wounds healed slowly and produced characteristic "white, deep, radiating scars, which we have so often seen in daily life" [20, p. 39]. It is noteworthy that Niemeyer observed how the gland disease (scrofula) and its surgical treatment could mark scrofulous patients with distinctive scars that were common in the late 19th century. Initially, a pig-like face, followed by stigmatizing radiating scars.

Geill, in parallel with Niemeyer, maintained that scrofula was not a disease "specific to the lungs but found in the intestines, joints, and most commonly in the glands" [21, p. 7]. Geill vividly described the journey of the tubercle bacillus: "The tubercle bacillus is absorbed by the lymph flow and transported to the glands, where it settles [...] if a child with particularly susceptible glands is affected, the glands will become tuberculous, and the child will become 'glandularly weak' (scrofulous)" [21, p. 8].

According to physician Carl Marinus Reisz (1829-1902), the tuberculous attack on tissue generally progressed "from gland to gland, until it forms a continuous lump [...] sometimes a gland is so rapidly and completely altered throughout its mass that it becomes impermeable" [24, p. 54]. Not unlike a sailor's tattoo, where the nearest "axillary gland fills with pigment, completely blocking further circulation in the gland, which becomes a barrier to the further progression of the pigment" [24, p. 55]. This could explain why tuberculosis remained localized in the nearest gland instead of spreading into the tissue, except in the neck, where the tubercular infection often migrated. When the glands in the neck were affected, the child developed "a familiar appearance with large, palpable knots on the neck, but if the glands of the chest or abdomen become tuberculous, the disease is not readily recognized by everyone" [21, preface].

Niemeyer argued that scrofula was a serious disease, demonstrating that "the disease can manifest anywhere, in organs and tissues, from the skin and mucous membranes to the deepest bones" [20, p. 48]. He approached this systematically and soberly:

The Skin

The skin was where "Glandular Disease most loves to appear," and it was "the part of the human body that is first affected [...] particularly on the hairy part of the head, the face, and behind the ears." Niemeyer believed that the hairy parts of the head and face were first affected because the body hair was "suitable for holding scabs and dirt." Scrofula presented as a "rash covered with thick, oozing yellow scabs" [20, p. 40]. The fluid irritated the skin and was contagious, necessitating care to prevent its spread to other parts of the body. It was essential "to observe the necessary cleanliness in time" and prevent scrofula from spreading "to larger and larger areas" [20, p. 40]. Again, attention was drawn to the face, as scrofula's pig-like face could develop from the hairy parts of the head and face into a "yellow-brown, oozing, and stinking mask" [20, p. 40]. Other manifestations of gland disease were also noted,

as scrofulous conditions could affect tissues beneath the skin. These presented as abscesses throughout the body, "sometimes located just beneath the skin and sometimes deep between the muscles." They ranged from pea to hazelnut-sized lumps that, "when they become 'mature,' have a dark bluish-red color." If the physician opened the abscess, "thin bloody matter flowed out," and the wound healed slowly [20, p. 41].

The Mucous Membranes

In addition to abscesses that appeared as swollen lumps under the skin, scrofulous mucosal disorders also occurred in the form of "chronic catarrhs with an exceptionally strong secretion of mucus with great persistence." The mucous membranes connected to the external skin "in the eye, at the corners of the mouth, the nose, and the ear" were at risk, and especially the nose could swell, giving patients a quite characteristic appearance; however, the stomach, intestines, and bronchial tubes could also be affected by catarrhs [20, p. 42].

Bones and Joints

On the arms and legs, scrofula manifested as swollen joints, "double joints," where the bones of the arms and legs could bend like wax under pressure. This was particularly evident on the shins, "so the sharp ridge of the shinbone protrudes like the edge of a saber" [20, p. 46]. Scrofula was not just about enlargements, but also inflammation — characteristic lumps — in the bones and joints themselves [20, p. 48]. Scrofula reached deeper, causing inflammation in bones and joints. It formed "lumps in the bone itself, filled with matter, gradually working their way to the bone's surface," from where they could open into surrounding muscle tissue and further out to the skin [20, p. 47]. If an inflammatory lump opened spontaneously, it did so very slowly, while it could also cause "sores that could persist for years with continuous discharge of thin, foul-smelling fluid." Even if the sore closed, there was no guarantee that "it would not reopen under certain circumstances," leaving scars that could impede natural movement in "the affected part of the body" [20, p. 48]. This scrofula was a chronic, fateful disease.

Aetiologies of Scrofula

Niemeyer emphasized the importance of scrofula as a distinct disease among other contemporary illnesses, such as rickets, as he considered scrofula to be "more intrusive in the human organism" [20, p. 48]. As mentioned, Niemeyer attributed the cause of the disease to the pathological composition of bodily fluids, specifically lymph — "the colorless fluid prepared in the intestinal canal from ingested nutrients" [20, p. 12]— as the localized origin of scrofula. In other words, the imbalance of lymph due to dietary intake was the direct cause of scrofula. Niemeyer termed an unhealthy composition of bodily fluids as scrofulous [20, p. 28], holding that scrofula was "in some cases [...] inherited," but in most instances, it was "surely acquired" through a child's "inappropriate treatment" or living conditions that either developed "possible predispositions for the disease or outright triggered it" [20, p. 28]. It was only when a patient became scrofulous, with lymph nodes swelling and becoming tender due to inflammation, that scrofula could be visually diagnosed. Glandular pain was not a good indicator of scrofula, but it was unnecessary, as visible glands were a reliable sign of the disease. Niemeyer distinguished between rapidly emerging glands in acute conditions, which were "generally very tender," and chronic conditions with a prolonged course, where "the glands could be completely painless" [20, p. 13].

In contrast, Geill vigorously advocated that scrofula was fundamentally a tuberculous infection, a view promoted and disseminated among colleagues following Robert Koch's (1843–1910) discovery of the tubercle bacillus in 1882. As early as 1865, French physician Jean-Antoine Villemin (1827–1892) described tuberculosis as a non-hereditary disease [22, p. 8], but it was only after Koch that the role of heredity in "the origin of pulmonary tuberculosis" [21, p. 9] was dismantled. According to Geill, the presence of the tubercle bacillus and a predisposition to disease in the form of a general state of weakness were necessary for scrofula to develop. Scrofula in "the mouth, nose, and facial skin" was explained by Geill as a "tuberculous affection" rooted in "tuberculosis in the tonsils" [21, p. 5]. The disease's array of symptoms in individual cases needed to be attributed to tuberculous infections, which starkly contrasted Niemeyer's explanation. Regarding the tubercle bacillus, the recognition that dried bacteria could survive "up to half a year outside the body" in a dry state meant that policymakers increasingly took an interest in the citizen's private home [21, p. 6]. Thus, bacteriological surveillance in society became a key element in the name of prevention.

Scrofula was understood by proponents of the tuberculous perspective as a chronic disease that, while originating as an infectious disease through a pathogen's influence, had been exacerbated by a "congenital or acquired state of debility" [21, p. 77]. Physicians were particularly attentive to individuals weakened by "overexertion, illnesses, childbed, etc." [21, p. 50]. Notably, "uncleanliness and poor skin care" were considered to contribute to a state of frailty, as "the skin participates in the work of expelling a large quantity of harmful metabolic products from the body" [21, p. 14]. The skin (and home) had to be kept clean and tidy, as this helped to prevent this unclean disease.

Geill believed that children's bodies should be gently hardened to raise their metabolism and provide at-risk children with the greatest possible resistance. It was crucial that the child received "plentiful, nourishing, and easily digestible food," allowed their lungs to inhale "fresh and clean air," and engaged in physical exercises to strengthen "respiratory muscles and stimulate blood

circulation," thereby promoting "nutrition" [21, p. 51]. This view aligned with Niemeyer, who asserted that a balanced relationship between "food and drink" on one hand and "physical movement" on the other [20, p. 25] was essential to ensuring a proper mixture of bodily fluids. Geill and Niemeyer concurred that healthy living required fresh air, skin care, nutrition, and physical activity.

Fresh Air

Fresh — and especially clean — air was considered "one of the greatest conditions for health," while poor, stagnant, and particularly humid air was viewed as "the absolute most harmful thing imaginable." Air was perceived as a "purifying agent for bodily fluids, as vital to the organism as the intake of nutrients" [20, p. 20]. Regarding the lungs and branches of the respiratory tract, Niemeyer asserted that catarrh occurred because the mucous membrane was "susceptible and exposed to the effects of poor air" [20, p. 44]. The relationship between fresh air and nutrition was expressed in the notion that a person could thrive "better on less good food when living in fresh air" than on excellent "nourishment while simultaneously residing in poor air" [21, p. 19]. Poor air was a primary cause of scrofula, emphasizing the importance of access to fresh air.

Skin Care

Niemeyer understood that what air was to the lungs, water was to the skin, and that glandular disease rarely developed "as long as one continues with baths." However, in practice, it often happened that parents ceased bathing the child after the first few weeks – especially if there were multiple children in the family. Niemeyer provides an example where a "doctor happens to prescribe a bath," only to observe that it was "something the child was not accustomed to at all" [20, p. 23]. This absence sometimes developed into a fear of water, despite the fact that most children were "not able to bear the consequences of this neglect without harm." In practice, the earlier parents stopped bathing their child – and deprioritized regular skin care — the earlier symptoms of scrofula appeared in the form of "eruptions on the body, face, or head" [20, p. 23].

Nutrition and Physical Activity

Just as the vital role of fresh air was crucial, poor diet was similarly perceived as one of the most decisive causes of scrofula, "when the body's nutritional fluids are already of poor quality" [20, p. 34]. Inadequate nutrition manifested even more quickly if the child was also "confined in rooms with poor air, where they also cannot get sufficient exercise" [20, p. 36]. Niemeyer wrote that "the affliction is essentially doubled" if glandular swellings occurred in the intestines, as this could lead to nutritional disturbances and digestive issues in the child [20, p. 7]. Thus, there was continuity between the naturopathic method, as represented by Niemeyer, and the pulmonary tuberculosis model presented by Geill, where scrofula was considered an infectious disease. This was evident in that both approaches placed particular emphasis on the social aspects of the disease, despite conflicting views on the etiology of scrofula. A key issue influencing treatment was whether scrofula could be inherited or acquired, and the general impact of (workplace) environment.

Treatments of Scrofula

Until 1865, scrofula was viewed solely as a hereditary disease, which meant that therapy was limited to symptomatic relief, such as stays in Madeira and Corsica to provide patients with sun and warmth, and notably the "extensive use of cod liver oil and Swedish Bitters" [24, p. 8]. Niemeyer argued that scrofula was best treated "by adhering to the general dietary guidelines" [20, p. 49]. This explains why only three of the book's 52 pages explicitly dealt with the treatment of scrofula, merging the content with previously mentioned points about fresh air, exercise, skin care, and nutrition. Niemeyer viewed scrofula as a "comprehensive constitutional disorder" that "is easier to prevent than to cure" [20, p. 52], resulting in a strong focus on preventive measures and practical guidance.

Niemeyer categorized scrofulous patients into two groups. The first was the obese patient, who had "a very peculiar appearance. The body is plump; the skin is puffy, lacking elasticity, and of a peculiar grayish-pale color; the lips are thick, protruding, and have a pale blue color." These obese patients were often from the wealthier classes, "whose children are allowed to fill themselves with all kinds of foods, without regard to their type or quantity" [20, p. 35]. The second group was the thin patient with a "slender build with transparent, white, thin, fine skin with little fat underneath; the cheeks have a peculiar fine red color; the muscles are weakly developed." The thin patients generally came from the "poorer population, who must live on potatoes, pork, and similar cheap dishes that can only be called nourishing to a certain extent" [20, p. 36]. There is an interesting contrast between the disease profile then and now, where the situation today is diametrically opposite.

At the 1890 International Medical Congress in Berlin, German bacteriologist and physician Robert Koch attempted to move beyond his discovery of the tubercle bacillus by introducing a new miracle remedy. Unfortunately, tuberculin proved to have no curative effect on tuberculosis in practice. Geill hoped that it would "be possible for us to find a remedy that can directly affect and kill the bacilli after they have entered the lungs and attacked them" [21, p. 71]. He also acknowledged that no miracle cure existed in 1890, despite high demand, as the "absolute cure" took not days and weeks, but months and years [21, p. 77].

According to Reisz, tuberculosis treatment in 1899 was characterized by its "complex nature." The Germans pursued results using tuberculin, but these immunity experiments were "rather naïve and thus only briefly

reported" [24, pp. 26-31]. Edoardo Maragliano's (1849–1940) and other Italians resorted to serum treatment, which gained attention between 1895 and 1898. Reisz admitted: "I cannot deny that this serum strikes me as highly suspect, and as I have already mentioned, the available reports make one inclined to consider it a thin and weak form of tuberculin." [24, p. 34]. Auriol and Sollaud, a French naval physician based in Cherbourg, treated patients using inhalation of sulfurous acid, reporting notably positive clinical outcomes [24, pp. 45-49]. Reisz concluded: "It is therefore not always easy to determine which element or elements in the chain of treatment is the primary remedy, or indeed how much each of the methods used contributes to the outcome of the treatment." [24, p. 78].

As mentioned, the medical miracle cure remained elusive, and treatment continued to focus on "raising the organism's strength and resistance by placing [the scrofulous child] under good hygienic and dietary conditions" [21, p. 75] to bring "the organism up from the predisposed state in which it has sunk" [21, p. 50]. This held no novelty, in line with Niemeyer's highlighted measures.

Geill's rationale was that a better composition of the blood and the vitality of individual cells enabled the lungs to establish an "impenetrable barrier against the tubercle bacilli's attack." This was achieved through "a cartilaginous capsule that excludes the tubercle bacilli from the surrounding healthy lung tissue," thereby depriving them of access to nutrients, which would ultimately extinguish the disease [21, p. 75]. This approach remained the only defense against the external aggressor until the development of the well-known Calmette vaccine (BCG), which remains the only partially protective vaccine against tuberculosis today. Geill highlighted, from an occupational health perspective, how the general spread of tuberculosis correlated with "the population's occupations and sources of employment, its poverty, and its vices" [21, p. 77]. Geill categorized "urban industry and factory work and alcoholism," which reduced the population's resistance, as modernity's iron cage, while "rural life, with its abundant outdoor movement, relatively easier access to appropriate food [*e.g.*, milk], and its lower propensity for drinking," was elevated as the optimal living conditions.

It is, however, noteworthy that heliotherapy and the therapeutic use of sunlight [27] – also widely promoted in southern European countries at the time, as noted above – are almost entirely absent from Dr. Niemeyer's and Dr. Geill's works. This limited attention suggests that sun-based treatments were not a central component of Danish scrofula management, in contrast to Mediterranean practices where heliotherapy featured prominently in both medical and public discourses. The omission in Danish sources may reflect climatic constraints or a cultural-medical preference for emphasizing air, hygiene, and nutrition over direct solar exposure.

Overall, the focus shifted from individual internal imbalance to the impact of the working family's environment, living, and working conditions. As is known, from 1875, medical reports were altered from pre-printed forms to include comment fields for describing the patient's hygienic conditions at home [25, p. 283]. This development occurred in parallel with the evolving understanding of the causes of scrofula, reflecting a broader public health movement in the latter half of the 19th century [26].

Bridging Historical Perspectives with Recent Advances in Contemporary Public Health

The historical discourse on scrofula highlights pivotal transitions in public health paradigms that resonate with contemporary understandings of disease and health. At the turn of the 20th century, scrofula's prevention and treatment relied heavily on the interplay between environmental, social, and individual factors. Fresh air, nutrition, and hygiene were emphasized not only as therapeutic measures but as essential public health strategies. This reflects an early acknowledgment of what we now recognize as the bio-psycho-social model, where health is viewed as an outcome of biological, psychological, and social determinants [28-31].

Scrofula, classified as a precursor to tuberculosis, also underscores the fusion of infectious and chronic disease paradigms; a theme that persists today [32-37]. Diseases like HIV/AIDS, initially acute and infectious, have transitioned into chronic, manageable conditions. Similarly, the intertwined narratives of infectious and non-communicable diseases (NCDs) illustrate the complexity of contemporary public health challenges, where socioeconomic factors and chronic comorbidities influence disease progression and outcomes. In this context, historical strategies for scrofula's prevention, such as improving living conditions and fostering intersectoral collaboration, resonate with modern efforts to address health inequities and social determinants. The early 20th century municipal hygiene reforms in Denmark foreshadowed today's holistic approaches to health promotion, bridging the gaps between medical interventions and societal well-being. These historical lessons remain relevant in addressing contemporary global health issues, reinforcing the importance of an integrated and adaptive public health strategy.

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Conflict of interest statement

The authors declare no competing interests.

Authors' contributions

UBK conceived the initial idea, conducted the historical analyses, drafted the first version of the manuscript, and contributed to subsequent revisions. CW and PK provided contemporary public health perspectives, contributed to the development of the initial concept, and critically reviewed manuscript drafts. All authors have read and approved the final version of the manuscript for publication.

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History of medicine and ethics

The penicillin revolution and the role of the forgotten pioneer Vincenzo Tiberio (1869-1915): discovery, development and legacy

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Keywords

Penicillin • Vincenzo Tiberio • Alexander Fleming • Antibiotics history • Mold-derived antimicrobials • Medical discoveries timeline

Summary

Penicillin's discovery is widely attributed to Alexander Fleming (1881-1955) Professor of Bacteriology at St. Mary's Hospital in London in 1928, who observed the antibacterial effects of Penicillium mold. Fleming found that his "mold juice" was capable of killing a wide range of harmful bacteria, such as streptococcus, meningococcus and the diphtheria bacillus. He then set his assistants, Stuart Craddock and Frederick Ridley, the challenging mission of isolating pure penicillin from the mold juice. It shown to be very unstable, and they were only able to prepare solutions of crude material to work with. Fleming published his findings in the British Journal of Experimental Pathology in June 1929, with only a passing reference to penicillin's potential therapeutic benefits. However, over 30 years earlier, Italian physician Vincenzo Tiberio (1869-1915) had conducted controlled studies on the bactericidal effects of mold extracts, publishing results that went largely unnoticed by the scientific community.This article runs through a work plan timeline and significance of early antimicrobial discoveries, tracing the overlooked work of Tiberio, Fleming's breakthrough, the biochemical properties of penicillin, and the wartime efforts that enabled its mass production. The story of penicillin is not only one of scientific innovation but also of missed recognition, collaboration, and the complex interplay of chance and preparedness.

Introduction

The discovery of antibiotics stands as one of the most transformative and consequential breakthroughs in the entire history of medicine. Before their introduction, bacterial infections – now often considered minor or easily treatable – were among the leading causes of mortality worldwide.

In the pre-antibiotic era, even seemingly trivial injuries such as a scraped knee, a dental abscess, or a mild surgical incision could spiral into life-threatening infections like sepsis. Diseases such as pneumonia, tuberculosis, syphilis, diphtheria, and scarlet fever claimed millions of lives annually.

Before its introduction there was no successful treatment and care also for infections such as gonorrhea or rheumatic fever. Hospitals were full of people with sepsis contracted from a cut, a scratch or abrasion and doctors did not have effective and decisive means or instruments; they could only wait and hope.

The absence of effective antimicrobial treatments meant that physicians were often powerless to intervene once an infection took hold. Clinical management consisted primarily of palliative care, basic antiseptic techniques, patient isolation, and in some cases, the use of toxic compounds that were only marginally effective and frequently harmful.

As a result, mortality rates for bacterial diseases remained unacceptably high, and medical interventions such as surgery, childbirth, or wound care were fraught with lethal risk. The advent of antimicrobial therapies in the 20th century represented a seismic shift. Not only did these drugs revolutionize the treatment of infectious diseases, they also transformed the practice of medicine itself. Suddenly, conditions that had long been untreatable became curable.

Life expectancy rose dramatically in many parts of the world, public health initiatives gained unprecedented efficacy, and medical fields such as surgery, oncology, and intensive care advanced rapidly due to the newfound ability to control postoperative and nosocomial infections. Antibiotics became the cornerstone of modern clinical practice, enabling complex medical interventions that would have been unthinkable just decades earlier. Among the many antibiotics discovered in the 20th century, penicillin occupies a singular place in medical history.

Penicillin, the first widely effective antibiotic, was discovered by Alexander Fleming in 1928 when he observed that a Penicillium mold inhibited bacterial

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growth [1, 2]. His findings, published in 1929, marked a turning point in medicine. However, this standard narrative often neglects earlier contributions, particularly those of Italian physician Vincenzo Tiberio, who reported similar antibacterial effects of mold extracts over thirty years before Fleming [2]. In 1895, Vincenzo Tiberio published a study on the antimicrobial effects of mold [3], inspired by the observation that mold on a family well reduced gastrointestinal infections. He hypothesized that mold released a substance inhibiting bacteria, anticipating later antibiotic concepts [4]. Largely ignored by Italy's scientific community [5], his work was rediscovered in the 20th century by Giuseppe Pezzi and others [6, 7], earning him overdue recognition in the history of penicillin.

Early Observations and Microbial Antagonism

Scientific interest in the antagonistic interactions between microorganisms – a concept now fundamental to microbiology, immunology, and pharmacology – emerged long before the formal discovery of antibiotics. As early as the mid-19th century, scientists began to hypothesize that microorganisms did not merely exist in isolation but could also influence, suppress, or even destroy one another. This idea, which would later be known as microbial antagonism, provided the conceptual groundwork for the development of antibiotic therapies. Early observations of these phenomena were scattered and often anecdotal, but they captured the imagination of a small group of pioneering scientists. Among the most influential figures in shaping this nascent understanding were Louis Pasteur (1822-1895) and Robert Koch (1843-1910), two titans of 19th-century bacteriology whose research fundamentally transformed the medical sciences. Pasteur's work on fermentation and his formulation of the germ theory of disease laid the intellectual foundations for understanding microbes as both causal agents of disease and, potentially, as biological tools that could be harnessed to control other harmful microorganisms [8].

Koch, through his methodical development of postulates and innovations in culturing techniques, established the link between specific pathogens and particular diseases, including tuberculosis and anthrax. Together, these scientists helped shift the perception of microbes from invisible nuisances to biologically active agents with profound implications for health and disease. Building on this evolving framework, Élie Metchnikoff (1845-1916), a Russian zoologist and immunologist working at the Pasteur Institute, introduced key insights into the defensive role of phagocytes in the immune system. He also extended the idea of microbial antagonism by noting how certain beneficial bacteria could suppress pathogenic strains within the gut microbiome. His observations on competitive exclusion anticipated the modern concepts of probiotic therapy and microbial balance, and his work was instrumental in demonstrating that microbial ecosystems could be modulated to promote health rather than simply sterilized to eliminate disease.

Fig. 1. Paul Ehrlich (1854 –1915) - [Public Domain. Wikipedia commons].

A critical leap in this field came with Paul Ehrlich (1854-1915), a German physician, microbiologist, and immunologist, who is often credited as the father of modern chemotherapy (in 1908, he received the Nobel Prize in Physiology or Medicine for his contributions to immunology) (Fig. 1).

Building on the idea that chemical agents could selectively target harmful microorganisms, Ehrlich developed the theory of the "magic bullet"—a compound that could eradicate a pathogen without damaging host tissues. His discovery of *Salvarsan* (arsphenamine) in 1909 as an effective treatment for syphilis marked the first successful application of this principle [9]. Although not an antibiotic in the contemporary sense — it was a synthetic arsenic-based compound — Salvarsan represented the first chemotherapeutic agent specifically designed to combat a microbial disease. Ehrlich's conceptual model not only bridged microbiology and pharmacology but also provided a scientific framework that would later guide the development of penicillin and other antimicrobial drugs. These foundational contributions underscore that the antibiotic revolution did not emerge in a vacuum, nor was it the result of a singular discovery. Rather, it was the culmination of decades of experimental work, theoretical innovation, and interdisciplinary dialogue. The understanding that microorganisms could act as both enemies and allies in human health laid the intellectual and experimental scaffolding for the advent of antibiotics - a leap that would be realized with penicillin in the 20th century, but whose roots lie deep in the scientific soil of the 19th.

Fig. 2. Vincenzo Tiberio (1869-1915) – (Naval medical officer of the Medical Corps of the Italian Navy) London [Public Domain. Wikipedia commons].

Vincenzo Tiberio: a Forgotten Pioneer

In 1895, Vincenzo Tiberio (Fig. 2), a young physician and medical officer in the Italian Navy, published an article titled *Sugli estratti di alcune muffe* ("On the Extracts of Some Molds") in the *Annali di Igiene Sperimentale*, a journal dedicated to experimental hygiene and public health research [3].

His investigation was driven by a keen empirical observation: at his uncle's home in Arzano, near Naples, he noticed a curious pattern. When the walls of the courtyard well—used for household drinking water—were periodically scraped clean of their natural mold layer, outbreaks of gastrointestinal illness, particularly enteritis, would spike among residents. Intrigued by this correlation, Tiberio hypothesized that the mold might play a protective role by inhibiting harmful bacteria in the water supply. To test this theory, he undertook a series of controlled experiments in a laboratory at the University of Naples. Demonstrating methodological rigor unusual for his time, Tiberio isolated several species of mold, including *Mucor mucedo*, *Penicillium glaucum*, and *Aspergillus flavescens*.

He then prepared *aqueous extracts* of these molds and subjected them to a series of *in vitro* assays against pathogenic bacteria, such as *Vibrio cholerae* – the agent responsible for cholera epidemics – and strains of *Staphylococcus*, which were known to cause wound infections and other illnesses.

His results were clear and replicable: the mold extracts exhibited a marked inhibitory effect on bacterial growth, both in culture media and, significantly, in *in-vivo* tests involving animal models [3].

Tiberio concluded that the molds released soluble substances into their environment with potent bacteriostatic and bactericidal properties – a hypothesis that, although he lacked the biochemical tools to isolate or characterize these compounds, foreshadowed the mechanism of action of antibiotics. Importantly, his paper included careful controls, thoughtful discussion of alternative explanations, and proposals for future research.

In many respects, it exemplified the ideals of early scientific microbiology and demonstrated an intuitive grasp of what we now understand as antimicrobial pharmacodynamics. Despite the strength of his data and the novelty of his hypothesis, Tiberio's work went largely unnoticed by the scientific establishment of his day. Several factors contributed to this neglect: his article was published in an Italian-language journal with limited international circulation; his position within the military medical service may have limited his academic visibility; and perhaps most critically, his findings were simply too far ahead of their time.

The dominant scientific paradigms of the late 19th century had not yet fully embraced the concept of inter-microbial chemical warfare or the therapeutic exploitation of microbial products. As a result, Tiberio's research was dismissed as anecdotal or overly speculative by contemporaries who failed to grasp its revolutionary implications. It was not until over half a century later, in the aftermath of World War II, that Tiberio's pioneering work was rediscovered by Giuseppe Pezzi.

In 1946, Pezzi published a commentary highlighting the significance of Tiberio's 1895 study and argued that it represented one of the earliest documented recognitions of mold-derived antibacterial substances [6].

This rediscovery, along with subsequent scholarly efforts to contextualize and re-evaluate Tiberio's research, finally began to secure his place in the history of antibiotic science. Modern historians and microbiologists now recognize Tiberio as a crucial but long-overlooked figure in the pre-history of antibiotics. His observations not only anticipated the discovery of penicillin by several decades but also demonstrated a scientific approach remarkably consistent with the principles of evidence-based medicine.

In retrospect, Tiberio's work stands as a powerful example of how scientific insight can be eclipsed by historical circumstance—and how rediscovering forgotten pioneers can enrich our understanding of medical progress [7].

Alexander Fleming and the Serendipitous Discovery

In 1928, Alexander Fleming, a bacteriologist at St. Mary's Hospital in London (Figs. 3, 4), made what is now regarded as one of the most serendipitous and pivotal discoveries in medical history. Upon returning from a holiday, Fleming noticed that one of his neglected Petri dishes, which had been inoculated with *Staphylococcus aureus*, had become contaminated with a colony of blue-green mold.

What caught his attention, however, was not the contamination itself, but the peculiar halo of inhibition surrounding the mold, in which no bacterial growth could be seen. Intrigued by this phenomenon, Fleming conducted a series of experiments and soon identified the

Fig. 3. Fleming in his laboratory, c. 1943 [Public Domain. Wikipedia commons].

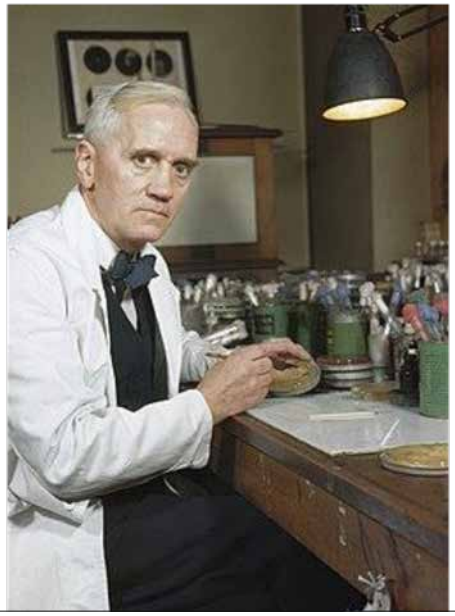
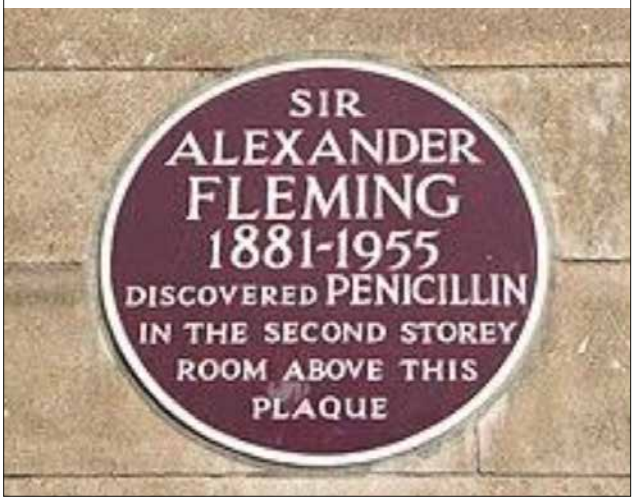


Fig. 4. Commemorative plaque marking Fleming's discovery of penicillin at St Mary's Hospital, London [Public Domain. Wikipedia commons].



mold as belonging to the genus *Penicillium*, specifically *Penicillium notatum* [2]. He deduced that the mold was secreting a substance into its surroundings that killed or inhibited the growth of bacteria. Fleming named this substance "penicillin," after the mold's genus, and published his findings in 1929 in the *British Journal of Experimental Pathology* [2]. His paper documented the antibacterial properties of penicillin against a variety of Gram-positive organisms, including *Staphylococcus* and *Streptococcus*, while leaving mammalian tissues unharmed. This selective toxicity - lethal to bacteria but safe for host cells - was an unprecedented pharmacological feature and would later become the cornerstone of antibiotic therapy. Despite the significance of his discovery, Fleming's ability to develop penicillin as a therapeutic agent was severely limited. The compound was inherently unstable and difficult to isolate in a pure and potent form. Fleming was a skilled microbiologist, but he lacked the chemical expertise and resources necessary to purify penicillin or determine its molecular structure. Moreover, his attempts to attract the interest of pharmaceutical manufacturers and the broader medical community were largely unsuccessful.

For more than a decade, penicillin remained a laboratory curiosity – a promising but impractical substance whose clinical potential was yet to be realized. The breakthrough came in the early 1940s, when a multidisciplinary team of researchers at the University of Oxford took up the challenge.

Led by the Australian pathologist Howard Florey and the German-born biochemist Ernst Boris Chain, and supported by the talented chemist Norman Heatley, the Oxford team set out to purify and stabilize penicillin for clinical use [9]. Building upon Fleming's foundational work, they developed extraction and purification methods that finally allowed penicillin to be produced in biologically active quantities. The team's preclinical studies demonstrated that penicillin was not only highly effective against a wide array of bacterial pathogens but also remarkably well tolerated by host organisms.

In 1941, they conducted the first human trials on patients suffering from life-threatening infections. The results were dramatic: patients who were on the verge of death from septicemia and abscesses began to recover within hours of receiving penicillin. However, early supplies were so limited that the drug had to be recovered from patients' urine and reused.

Recognizing its extraordinary therapeutic potential, Florey and Chain urgently sought means to scale up production. This marked the beginning of a massive international effort to industrialize penicillin manufacturing, especially as World War II created an acute need for effective antimicrobial agents on the battlefield. The Oxford team partnered with scientists and government agencies in the United States, including the USDA and pharmaceutical companies such as Pfizer, to optimize fermentation techniques and boost yields.

These collaborative efforts led to the development of deep-tank fermentation and the eventual mass production of penicillin, which became widely available to Allied troops by 1944 [9].The contributions of Florey, Chain, and their collaborators were so critical to the practical realization of penicillin's promise that they were awarded the Nobel Prize in Physiology or Medicine in 1945, alongside Fleming. While Fleming had discovered penicillin, it was Florey and Chain who transformed it into a usable, life-saving drug - an achievement that would usher in the modern antibiotic era and save countless lives.

Mechanism of Action and Pharmaceutical Development

Penicillin exerts its potent antibacterial effects through

a highly specific mechanism that targets one of the most vital structures in bacterial physiology: the cell wall. The bacterial cell wall is primarily composed of peptidoglycan, a complex polymer consisting of sugar chains cross-linked by short peptides. This mesh-like structure provides mechanical strength and osmotic stability, enabling the bacterium to withstand the high internal pressure generated by its cytoplasm. Without an intact cell wall, most bacteria cannot survive.

The final stages of peptidoglycan synthesis are mediated by a class of enzymes known as transpeptidases, which are part of a broader group collectively referred to as penicillin-binding proteins (PBPs). These enzymes catalyze the formation of peptide cross-links between adjacent strands of peptidoglycan, effectively "sealing" the wall during bacterial growth and division. Penicillin, a β-lactam antibiotic, inhibits this critical enzymatic step by irreversibly binding to the active site of PBPs, thereby halting the cross-linking process and compromising the structural integrity of the cell wall [10].

The molecular secret of penicillin's action lies in its β-lactam ring, a four-membered cyclic amide that mimics the terminal D-Ala-D-Ala dipeptide of the peptidoglycan precursor - a natural substrate for PBPs. This molecular mimicry enables penicillin to "trick" the enzyme into forming a covalent bond with the β-lactam ring, rendering the PBP permanently inactivated. As a result, the bacterium cannot synthesize new peptidoglycan nor repair existing damage, particularly during cell division when the demand for new cell wall material is highest.

The outcome is osmotic lysis, as the weakened cell wall can no longer resist the internal turgor pressure, leading to rupture and cell death. What makes penicillin especially remarkable is its selectivity. The targets of penicillin – PBPs and peptidoglycan – are unique to prokaryotic organisms and entirely absent in eukaryotic cells, including those of humans and animals. This means that penicillin can be used to kill or inhibit bacterial pathogens without harming host tissues, a pharmacological ideal known as selective toxicity [11].

This property set penicillin apart from earlier antimicrobial approaches, such as antiseptics and heavy-metal compounds, which lacked specificity and often caused significant collateral damage to host cells. Furthermore, the discovery of penicillin's mode of action contributed to a broader understanding of bacterial physiology and spurred the development of entire classes of structurally related antibiotics, including cephalosporins, carbapenems, and monobactams – all of which share the β-lactam core and exploit the same biochemical vulnerability. These β-lactam antibiotics differ in spectrum, stability, and resistance profiles, but their common mechanism continues to serve as a foundation for treating a wide array of bacterial infections.

Beyond its immediate clinical utility, penicillin's mechanism also had a profound impact on molecular biology and pharmacology. It provided the first clear example of an antibiotic that interferes with a specific bacterial target through a defined chemical interaction, laying the groundwork for rational drug design. It demonstrated that microbial metabolism could be selectively disrupted without compromising host integrity, thus ushering in a new era of targeted therapeutics and precision pharmacology.

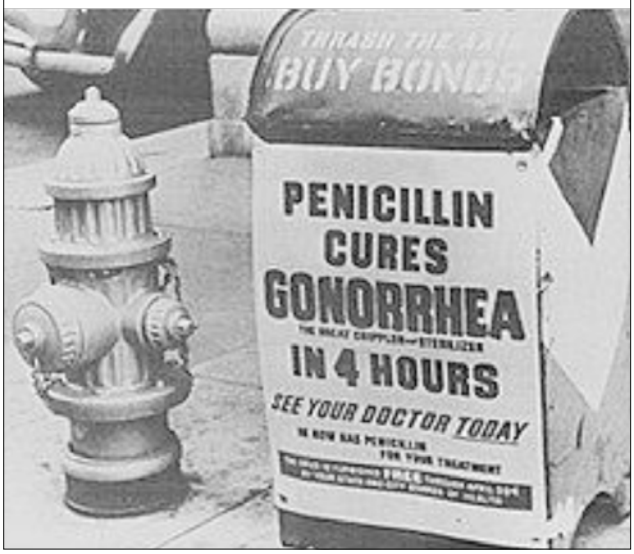
In summary, penicillin's mode of action - centered on the inhibition of transpeptidases and the collapse of peptidoglycan synthesis - is a masterclass in pharmacological precision. Its elegance lies not only in its biochemical efficacy but also in its evolutionary exploitation of a fundamental bacterial vulnerability, all while sparing the host. This combination of potency, specificity, and safety transformed penicillin into the prototypical antibiotic and set the standard by which future antimicrobials would be judged [11].

Industrial Production and Wartime Expansion

World War II served as a crucial accelerant in the transformation of penicillin from a laboratory curiosity into a mass-producible and strategically vital therapeutic agent. In the late 1930s and early 1940s, as global conflict escalated, the demand for effective treatments for battlefield infections became urgent. Wounds sustained in combat were frequently complicated by bacterial contamination, leading to sepsis, gangrene, and high mortality rates. While sulfonamides offered some relief, their efficacy was limited against several key pathogens. The search for a more powerful antimicrobial agent gained urgency and soon centered on the promising but underdeveloped compound known as penicillin. Initial efforts in the United Kingdom were hampered by wartime resource shortages and the bombing of British infrastructure. Despite the Oxford team's success in demonstrating the therapeutic potential of penicillin through animal studies and early human trials, their laboratory-scale production could not meet the pressing medical demands of a world at war. Recognizing the limitations of domestic facilities, Florey and his colleague Norman Heatley made a strategic journey to the United States in 1941 to seek support for large-scale production. Their appeal was received with enthusiasm by American scientific and governmental institutions.

The U.S. Department of Agriculture's Northern Regional Research Laboratory (NRRL) in Peoria, Illinois, was selected as the center of this effort due to its expertise in industrial microbiology and fermentation technologies. There, researchers began optimizing fermentation conditions to increase penicillin yields. A pivotal breakthrough came when they replaced the traditional surface culture method with submerged (deep-tank) fermentation, a more scalable and controllable technique. In this process, mold cultures were grown in large, aerated tanks, dramatically increasing output compared to the shallow tray systems used in earlier trials. One of the most serendipitous contributions to the program came from Mary Hunt, a laboratory technician at NRRL. Tasked with finding more productive strains of *Penicillium*, she brought in a moldy cantaloupe from

Fig. 5. An advertisement advertising penicillin's "miracle cure" [Public Domain. Wikipedia commons].



a Peoria market.

The mold growing on its rind, later identified as Penicillium chrysogenum, was found to be significantly more productive than Fleming's original *P. notatum* isolate. The NRRL team designated this high-yielding strain as NRRL 1951, and it became the genetic foundation for all subsequent industrial penicillin production [9]. To push yields even higher, scientists at NRRL and collaborating pharmaceutical companies employed X-ray and ultraviolet mutagenesis, exposing the fungus to radiation to induce beneficial genetic mutations. This process led to the development of mutant strains capable of producing penicillin at levels more than 1,000 times greater than the original mold. Meanwhile, chemical engineers and microbiologists worked hand-in-hand to optimize every stage of the fermentation process, including aeration, temperature control, nutrient composition, and extraction methods.

The collaboration between academic researchers, government agencies, and private industry – including major pharmaceutical firms such as Pfizer, Squibb, and Merck – was unprecedented in scale and coordination. These companies rapidly adapted their facilities to accommodate the deep-tank fermentation method, effectively creating the first global-scale antibiotic manufacturing infrastructure. By mid-1944, in time for the D-Day invasion of Normandy, penicillin was being produced in quantities sufficient to treat thousands of Allied soldiers. It was distributed to military hospitals across Europe and the Pacific, where it dramatically reduced mortality from wound infections, pneumonia, and venereal diseases such as syphilis and gonorrhea [7] (Fig. 5).

The wartime success of penicillin production not only changed the outcome for countless soldiers but also established a new model for pharmaceutical innovation. It demonstrated the potential of public-private collaboration, government-sponsored research initiatives, and the industrial scalability of biological products. Furthermore, it marked the beginning of what would later be called the antibiotic revolution, laying the groundwork for post-war drug development and the broader transformation of medicine in the second half of the 20th century.

Legacy, Resistance, and Future Challenges

Penicillin's spectacular success in the 1940s did not merely save lives—it also catalyzed a revolution in medicine and public health, ushering in what is now referred to as the "golden age of antibiotics." This period, spanning approximately from the mid-1940s to the early 1970s, witnessed the rapid discovery and commercialization of multiple new classes of antibiotics, each addressing different bacterial targets and broadening the spectrum of treatable diseases. Among the most impactful were streptomycin, the first aminoglycoside antibiotic and the first effective treatment for tuberculosis [11]; tetracycline, which provided broad-spectrum activity against Gram-positive and Gram-negative organisms; and chloramphenicol, a powerful agent effective against life-threatening infections such as typhoid fever and meningitis [12]. Together, these antibiotics transformed clinical practice. Mortality from bacterial diseases plummeted in both developed and developing countries. Conditions that were once fatal or untreatable—such as bacterial endocarditis, septicemia, and osteomyelitis—became manageable. In hospitals, the availability of antibiotics enabled more aggressive surgical interventions, including organ transplants, cancer resections, and joint replacements, by drastically reducing the risk of postoperative infections.

In obstetrics and neonatology, antibiotics helped curb maternal and infant mortality associated with puerperal fever and neonatal sepsis. Public health campaigns and vaccination efforts now had a reliable pharmacological partner, allowing for the integrated control of many communicable diseases. However, the very success of antibiotics sowed the seeds of an emerging crisis. Widespread and often indiscriminate use—in clinical settings, agriculture, animal husbandry, and even household products—created intense selective pressures that favored the survival of resistant bacterial strains. One of the earliest and most formidable forms of resistance was the bacterial production of β-lactamases, enzymes capable of hydrolyzing the β-lactam ring of penicillin and rendering it ineffective [13]. These resistance mechanisms spread rapidly via horizontal gene transfer, turning once-treatable pathogens into stubborn clinical challenges. In response, pharmaceutical scientists developed second- and third-generation β-lactam antibiotics – including cephalosporins, monobactams, and carbapenems – designed to evade enzymatic degradation. Additionally, β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam were formulated to protect primary β-lactam antibiotics from

destruction. These combinations temporarily restored the efficacy of older drugs, but the arms race between pharmaceutical innovation and microbial adaptation was only accelerating. By the late 20th and early 21st centuries, a new and deeply concerning pattern emerged: the rise of multidrug-resistant organisms (MDROs), against which few, if any, antibiotics remained effective. Among the most infamous are methicillin-resistant Staphylococcus aureus (MRSA), which causes severe hospital- and community-acquired infections; vancomycin-resistant enterococci (VRE); and carbapenem-resistant Enterobacteriaceae (CRE), sometimes dubbed "superbugs" due to their extreme resistance and high mortality rates. These pathogens have led to prolonged hospital stays, increased healthcare costs, and a resurgence in mortality from infections previously considered curable. The World Health Organization (WHO), alongside the Centers for Disease Control and Prevention (CDC) and other international agencies, has declared antimicrobial resistance (AMR) one of the top ten global public health threats. According to recent projections, if unchecked, AMR could cause 10 million deaths annually by 2050, eclipsing mortality from cancer and cardiovascular disease [14-16]. Addressing this looming catastrophe requires a comprehensive and coordinated response. At the clinical level, antibiotic stewardship programs are essential to ensure the judicious use of existing antimicrobials, guided by microbiological diagnostics and resistance surveillance. Moreover, several natural antibiotics have been shown to evolve as part of microbial competition in the environment [17].

At the policy level, regulatory frameworks must restrict the non-therapeutic use of antibiotics in agriculture and enforce prescription guidelines in human medicine. Moreover, research incentives and public-private partnerships are urgently needed to reinvigorate antibiotic discovery, particularly since pharmaceutical companies have largely abandoned antibiotic development due to low profitability and high regulatory hurdles. Beyond technical solutions, combating AMR demands global coordination. Resistance knows no borders, and efforts in one country can be undermined by inaction in another. International collaborations such as the Global Antimicrobial Resistance Surveillance System (GLASS), the One Health initiative, and the GARDP (Global Antibiotic Research and Development Partnership) are steps in the right direction, but they require sustained funding, political commitment, and public engagement [18]. In essence, the rise of antibiotic resistance is a stark reminder that scientific breakthroughs, no matter how powerful, are not immune to the consequences of overuse and neglect. The legacy of penicillin is thus twofold: it exemplifies the life-saving potential of biomedical innovation and the ongoing challenge of preserving that legacy in a rapidly evolving microbial world.

Conclusion

While Fleming is rightfully credited, the early work of figures like Tiberio reminds us that the path to discovery is often long, collaborative, and overlooked. Penicillin's story is one of scientific brilliance, global mobilization, and the delicate balance between therapeutic innovation and microbial adaptation. As we navigate the antibiotic resistance crisis, these lessons are more urgent than ever.

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Informed consent statement

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Conflicts of interest statement

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

Authors' contributions

conceived the study: FMG, EV, LI; designed the study: EV, FMG, LI; drafted the manuscript: EV, FMG; performed a search of the literature: MM, LG, LI; critically revised the manuscript: MM; conceptualization and methodology: FMG, EV, MM, LG, LI; investigation and data curation: LG, EV, LI; original draft preparation: EV, FMG; review: MM, EV; editing: MM, FMG, EV, LI All authors have read and approved the latest version of the paper for publication.

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