Reducing preventable deaths: Health education and policy

Edited by
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Reducing preventable deaths: Health education and policy

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Actual Causes of Death in Relation to Media, Policy, and Funding Attention: Examining Public Health Priorities

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Despite numerous public health advancements over the last century, we continue to under-invest in prevention and public health efforts. As a result, one of the most challenging aspects of public health is prioritizing the use of limited resources. Building on the foundation of previous researchers, the goal of this exploratory study was to provide current estimates for the actual causes of death, media attention, policy focus, and research funding in the United States. In addition, we sought to calculate and compare media attention, policy attention, and research funding trends to better assess the nation's prioritization of health issues. Using a systematic approach, we searched available databases, including Media Cloud, Nexis Uni, Congress.gov, and the Department of Health and Human Services Tracking Accountability in Government Grants System from January 1, 2010-December 31, 2019 and compared how the actual causes of death in the United States align with health-related media attention, policy attention, and federal spending. Overall, our findings suggest that our priorities are not well-aligned with the actual causes of death. Certain actual causes appear to be consistently misaligned across media, legislative, and financial sectors (e.g., tobacco). This work highlights the importance of multiple strategies—media coverage, national legislation, and government spending—as indicators of public health attention and priorities. These results may inform discussions about how to best allocate U.S. public health resources to better align with the actual causes of death.

Keywords: actual causes of death, prioritization, resource allocation, media, policy, funding

INTRODUCTION

Over the last century, public health has contributed to drastic reductions in mortality and morbidity. In spite of these advancements, we continue to under-invest in prevention and public health efforts (1). In 2018, the United States spent $3.6 trillion dollars on healthcare, ~18% of the country's gross domestic product (2). However, <3% of total healthcare spending in the United States is dedicated to public health and prevention each year (3–5). In 2018, this equated to an average of $10,874 per person in treatment costs, compared to only $286 per person in prevention efforts (6).

Underinvestment in prevention and limited resources often require decision makers to place priority on some efforts over others. There are several factors influencing prioritization. One way to determine priority is the simple quantification of the problem. When quantifying and prioritizing

public health issues, there are many different scientific measures, including counting total deaths, preventable deaths, DALYs (disability-adjusted life years) and QALYs (quality-adjusted life years) (7, 8). Another factor that may shift priorities for resource allocation is media attention, which can influence awareness of certain health issues (9, 10). This, in turn, can shape the public's perception of current health issues (11). Policy legislation—both proposed and enacted—is another measure of the extent of public health action. Finally, government funding allocated for prevention and public health is an indicator of the relative priority of an issue.

Each of these indicators—media coverage, national policies, and government spending—are intertwined within the policy process. Howlett and Ramesh outline the policy process in the following steps: defining the problem; agenda setting; policy formulation; policy implementation; and policy evaluation (12). Though many scholars acknowledge the oversimplification of the policy process within this model (13), it can be helpful in this case when considering how media, national policies, and government spending fit within the complex policy process. Media attention can greatly impact early stages in the policy process, such as agenda setting (14–17), as well as policy formulation, evaluation, and termination (18). Policy development and implementation consequently impact government spending for health-related issues (19). As a result, media coverage, national legislation, and government spending may be related—but distinct—indicators of the nation's public health priorities.

Using recent infectious diseases as an example, we can examine how prioritization in media, policy, and research spending can interact to influence a public health issue. The novel Coronavirus disease (COVID-19), a community-spread respiratory illness, was first detected in China but has since spread to more than 100 countries worldwide, reaching pandemic status and receiving substantial media attention in the United States (20–23). By May 1, 2020, after the virus had exceeded containment measures, more than 70 new pieces of legislation were brought before Congress, one of which was passed (24). This piece of legislation provided $8.3 billion in funding for COVID-19 control and research through federal agencies. Given the large-scale impact of COVID-19 in the United States (25), multiple strategies (media, legislation, and government funding) have been used to target a public health crisis. Though the vast impacts of this pandemic are ongoing, COVID-19 provides an example of quickly mobilizing national resources to impact an emerging infectious disease.

A combination of strategies, such as media, policy, and funding, can also affect chronic disease prevention and control efforts [e.g., obesity, tobacco, cancer early detection; (26–28)]. For example, beginning in 1989, California's tobacco control initiative funded two primary strategies to decrease smoking rates—media and policy advocacy (29). The efforts included mass media campaigns, statewide cigarette taxes, and increased funding for prevention and treatment programs. The combined approach resulted in decreased smoking prevalence (29).

In 1993, McGinnis and Foege described the burden associated with the leading causes of death in the United States and analyzed the underlying modifiable risk factors (30). They named these

factors the "actual causes of death" and estimated the annual total number of deaths due to each actual cause. One of the primary lessons from this study was the need for a greater emphasis on prevention efforts, as well as a redistribution of public health resources in the United States (30). Mokdad et al. updated the data in 2004 and found that the leading actual causes of death for U.S. residents were tobacco (435,000 deaths/year), diet/physical activity (400,000 deaths/year), and alcohol consumption (85,000 deaths/year) (31). From these estimates, we see that the top four actual causes of death are responsible for nearly 40% of all annual deaths in this country. Given that many of the actual causes of death are modifiable risk behaviors with underlying environmental and policy determinants (32), this presents an excellent opportunity for examining health priorities and potential interventions. However, there has, to our knowledge, been no further exploration of coverage of health topics and policy actions compare with the actual causes of death.

Increased media attention, policy mandates, and government-funded research contribute to the control and containment of large-scale public health concerns, but the prioritization of resources may differ from actual causes of death. For example, there may be variations in resource allocation based on the amount of media attention between emerging infectious diseases and chronic diseases. Since resource allocation decisions are complex, we need to explore how other contributing factors, such as media attention, legislation, and spending, align with the actual causes of death.

Building on previous research (30, 31), the goals of this study were two-fold. First, we used a systematic approach to provide current estimates for the actual causes of death, media attention, policy attention, and research funding in the United States. Next, we described how the actual causes of death in the United States align with health-related media attention, policy attention, and federal spending.

MATERIALS AND METHODS

Search Strategy

The search terms included in this review were informed by the nine categories described by McGinnis and Foege—tobacco; poor diet and physical inactivity; alcohol consumption; microbial agents; toxic agents; motor vehicles; firearms; sexual behavior (e.g., sexually transmitted diseases and HIV); and illicit drug use (30). However, for the purposes of this paper, we separated *poor diet* and *physical inactivity* to analyze the risk factors independently, since they are independent risk factors for multiple chronic diseases (33). Beyond that change, we used the original categories provided by McGinnis and Foege for this analysis; updating the original categories was beyond the scope of this work. Then MeSH terms with similar meanings were added to ensure a more inclusive search; see **Supplementary Table 1** for a complete list of terms. These search terms were applied to the following databases: the Institute for Health Metrics and Evaluation (IHME) (34), Media Cloud (35), Nexis Uni (36), Congress.gov (24), and the Department of Health and Human Services (HHS) Tracking Accountability in Government Grants System (TAGGS) (37). All database

searches were restricted by geography, language, and time frame; that is, only results that were published in the United States (i.e., 50 states and Washington, D.C.), written in English, and distributed from January 1, 2010–December 31, 2019 were analyzed. More detail regarding search strategies is provided in **Supplementary Table 2**.

Actual Causes of Death

The IHME, a website which provides population-level health data as part of research being conducted at the University of Washington, was used to update total deaths due to the actual causes of death (34). The Global Burden of Disease Compare feature provided 2017 data regarding deaths attributable to each actual cause of death in the United States. Individual searches were completed for each cause of death using the previously described search terms. The IHME database houses information for all deaths and classifies them as either direct *causes of death* or *risk factors,* which refers to potentially modifiable factors (34). The majority of the actual causes of death were classified by the IHME as *risk factors* with the exception of *microbes, motor vehicles,* and *firearms,* which were classified as *causes of death.* This difference in classification did not affect the search strategy but may be useful if trying to replicate study findings.

Media

Media Cloud and Nexis Uni were selected as databases for media analysis. Media Cloud was chosen because it specializes in tracking online media presence, while Nexis Uni provides data on a variety of media, including national- and local-level newspapers. These two databases were chosen to create a more comprehensive, complementary approach to media analysis. The Media Cloud database encompasses online news stories, as well as hyperlinks, Bitly clicks, and social media shares from more than 60,000 online sources (35). Using the Explorer function of Media Cloud, we included both U.S. national and state/local parameters into our search and tracked the total number of daily occurrences for each cause of death from 2010 to 2019 using the previously described search terms. We calculated the total number of search results per year and created an overall average for each cause of death. Nexis Uni results, derived from more than 15,000 sources (36), were filtered by publication type to include only newspapers and newswires/press releases. We recorded the total number of references to each actual cause of death each year and averaged the totals. Finally, we used a Spearman rank correlation, a non-parametric measure of the strength and direction of an association between two variables, to examine the relationship between the number of deaths per year and the amount of media attention in both Media Cloud and Nexis Uni databases. Each result from these databases was given equal weight during analysis, as the goal was to analyze the overall quantity of media attention.

Policy

Congress.gov was selected as a source of data because it allowed us to restrict our search to only legislation [i.e., no congressional records, treaty documents; (24)]. We then compared the statuses (i.e., legislation introduced vs. legislation that became law) and

rates of legislation across the actual causes of death. Total numbers of proposed and passed legislation were calculated for January 1, 2010–December 31, 2019, and an overall average was calculated. Finally, we ranked the causes of death by number of proposed and passed legislation and conducted a Spearman rank correlation to assess the alignment with the number of deaths per year. Because our goal was to analyze overall quantity of proposed and passed legislation, each result from this database was given equal weight during analysis.

Federal Funding

TAGGS, a website that compiles financial assistance (i.e., grants and contracts) provided by the HHS Operating Divisions and the Office of the Secretary Staff Divisions (37), was selected as a way to gauge government spending on research and development. It is important to note that the search strategies for this particular database differed from the others, so the search terms were modified slightly. For example, truncated terms were not permitted in TAGGS. As a result, all truncated search terms were spelled out fully and listed (e.g., "pollute" and "pollution" instead of "pollut*"). Next, we were unable to narrow searches using Boolean operators, so terms that yielded irrelevant results were removed. For example, "shotgun" and "gun" search terms were removed from the *firearms* category because the terms yielded only funding related to aging (e.g., "whole genome shotgun sequencing") and biotechnology (e.g., "electron gun"). Similarly, "cancer" was removed from the *sexual behaviors* category because it yielded results related to all forms of cancer—not just cancer related to sexual behavior (e.g., lung cancer). These terms would have skewed the appearance of funding opportunities related to firearms and sexual behaviors; all other search terms remained the same. The total amount of available funding per year was calculated for 2010–2019, and an overall average was calculated. Once again, we ranked the causes of death by amount of research funding allotted and conducted a Spearman rank correlation to assess the alignment with the number of deaths per year.

Finally, we calculated z-scores for each actual cause of death based on the ratio of number of totals deaths and the recorded media, policy, and federal funding presence using the following formula: $Z = (x - \mu)/\sigma$. We first calculated a ratio between the total number of deaths (e.g., tobacco = 440,000) and the average amount of media, policy, or government spending for that cause of death. This ratio served as our raw score (x). Next, we subtracted the sample mean (μ) (i.e., the average of all ratios across all causes of death) from the raw score and divided by the population standard deviation (σ). These data provided a way to standardize scores across categories and directly compare the degree of misalignment between media, policy, and federal funding.

RESULTS

Actual Causes of Death

First, we looked at the totals for causes of death, media attention, legislation, and government spending over time; the goal was to assess patterns and provide descriptive information. **Table 1** presents a side-by-side comparison of the estimated totals for the

TABLE 1 | Estimated number of deaths for each actual cause of death in the United States 1990, 2000, 2017.

Cause of death	No. (%) in 1990[a]	No. (%) in 2000[b]	No. (%) in 2017[c]
Tobacco	400,000 (19)	435,000 (18)	440,000 (16)
Poor diet	300,000 (14)	400,000 (17)	503,000 (18)
Physical inactivity			73,000 (3)
Alcohol	100,000 (5)	85,000 (4)	81,000 (3)
Microbial agents	90,000 (4)	75,000 (3)	113,000 (4)
Toxic agents	60,000 (3)	55,000 (2)	201,000 (7)
Motor vehicles	25,000 (1)	43,000 (2)	30,000 (1)
Firearms	35,000 (2)	29,000 (1)	40,000 (1)
Sexual behavior	30,000 (1)	20,000 (1)	14,000 (1)
Illicit drug use	20,000 (<1)	17,000 (1)	105,000 (4)

[a] Total of 2,148,463 deaths in the United States.
[b] Total of 2,403,351 deaths in the United States.
[c] Total of 2,813,503 deaths in the United States.

actual causes of death collected by McGinnis and Foege (30) and Mokdad et al. (31), and the updated totals from IHME in 2017. As illustrated in **Table 1**, the total number of deaths from some causes, such as tobacco, has remained relatively stable from 1990 to 2017, while others, such as deaths from sexual behaviors, have decreased since 2000. Deaths related to toxic agents and illicit drugs have increased by more than 300 and 600%, respectively, since 2000. We then compared media coverage, legislation, and government spending with rankings of the 2017 actual causes of death in the United States.

Media

The media search results between Media Cloud and Nexis Uni were not entirely aligned. Media Cloud, which collected media attention from a variety of sources at the national and local levels, suggested that media attention for the actual causes of death has increased steadily over time (see **Supplementary Table 3** for detailed information). As displayed in **Figure 1**, when comparing the rankings between the actual causes of death and our Media Cloud search, there was a slight negative correlation ($r_s = -0.02$). In addition, poor diet and motor vehicles received the largest amount of media attention out of the actual causes of death on average (1,103,447 and 981,693 occurrences/year, respectively). However, motor vehicle deaths were relatively low in terms of mortality totals, accounting for <1% of all deaths in the United States. Tobacco received the lowest amount of attention on Media Cloud (168,706 occurrences/year), despite the fact that it was responsible for nearly 16% of all deaths in the United States in 2017. Similarly, our search criteria revealed that references to firearms appear in Media Cloud an average of 841,236 times/year. This is more media attention on average than tobacco, toxic agents, and microbial agents receive *combined*.

Our findings from the Nexis Uni database suggested that the cumulative media presence for the actual causes of death was relatively stable or has even decreased from 2010 to 2019 (see **Supplementary Table 4** for detailed information), with a small, positive correlation ($r_s = 0.18$) between the actual causes of

death and the Nexis Uni rankings. As shown in **Figure 2**, on average, sexual behavior, alcohol, and tobacco received the least media attention (41,541; 59,033; and 69,027 occurrences/year, respectively), while poor diet and motor vehicles received the most (283,053 and 205,656 occurrences/year, respectively). These results also show that the amount of media attention does not align with the total number of deaths per year. For instance, diet received more than four times as much media attention as tobacco did on average, despite the comparable death totals. In addition, illicit drug use generally received more than twice the media coverage that tobacco did, despite the fact that tobacco was responsible for nearly four times as many deaths.

Policy

The numbers of both proposed and passed legislation have remained relatively consistent from 2010 to 2019 for each actual cause of death (see **Supplementary Tables 5**, **6** for detailed information). As shown in **Figure 3**, results revealed a small, positive correlation ($r_s = 0.27$) between the actual causes of death and proposed legislation in the United States. The highest total number of proposed policies related to poor diet and physical inactivity, which elicited an average of 1,341 and 1,267 policy proposals/year, respectively. Alcohol, firearms, and tobacco, on the other hand, produced an average of 440, 428, and 398 policy proposals each year. Tobacco received only one-third of the total number of policy proposals compared to illicit drug use, despite a greater number of deaths being attributable to tobacco.

When comparing passed legislation with the actual causes of death, there was a small, positive correlation ($r_s = 0.19$), which is illustrated in **Figure 4**. On average, policies related to physical inactivity, poor diet, and illicit drug use had the highest approval totals (average of 50, 42, and 42 each year, respectively). Policies which had the lowest average number of approvals involved sexual behavior (20 policies/year), firearms (20 policies/year), alcohol (19 policies/year), and tobacco (17 policies/year). In 2017, physical inactivity and illicit drug use were responsible for a combined average of 178,000 deaths, which is significantly less than the deaths attributed to tobacco. However, more than double the number of policies were enacted each year for both physical activity and illicit drug use than for tobacco.

Federal Funding

As shown in **Figure 5**, there was a small, positive correlation between the actual causes of death and federal funding ($r_s = 0.16$). For certain causes of death, the amount of federal funding dedicated to research and development has changed drastically over time (see **Supplementary Table 7** for detailed information). For example, federal funding related to physical inactivity and sexual behaviors has remained relatively stable since 2010, while research related to illicit drug use has nearly doubled since 2010. Funding surrounding poor diet, on the other hand, has decreased ~33% between 2010 and 2019. An average of $5.4 billion was allotted to research surrounding sexual behaviors each year, making it the highest-funded actual cause of death. Similarly, an average of $4.4 billion in research funding was dedicated to illicit drug use, as well as $4.1 billion dedicated to microbial agents. Tobacco, the second leading actual
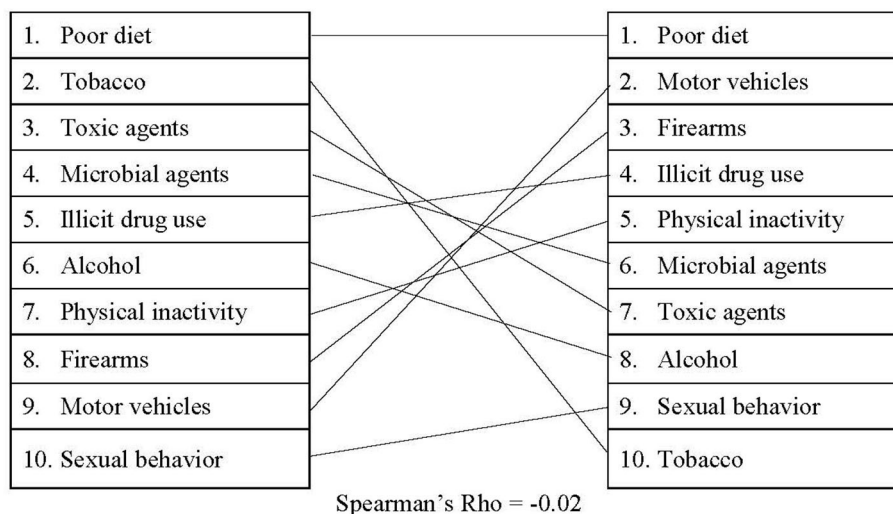
FIGURE 1 | Comparing actual causes of death to Media Cloud presence.
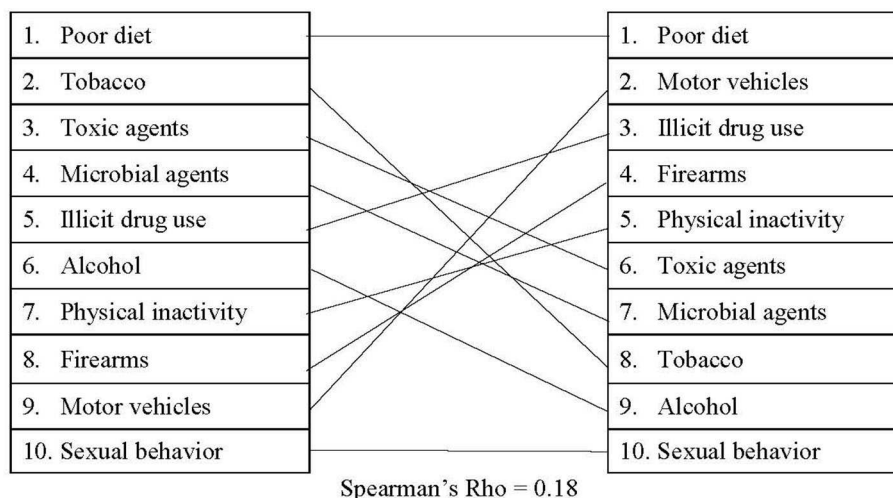
FIGURE 2 | Comparing actual causes of death to Nexis Uni presence.

cause of death in the United States, received <10% of the total budget allotted for sexual behavior research. Despite the fact that firearms were responsible for ~40,000 deaths in 2017, firearms research received only $900,000 on average over the last 6 years. In fact, from 2010 to 2014, there was no grant money awarded for firearms research using our search criteria.

Finally, we compared the rankings and relative weights of the actual causes of death, media attention, policy attention, and government spending over time. **Table 2** presents the simple rankings for each cause of death across categories, while **Figure 6** presents the findings of standardized rankings, which were calculated using z-scores. This allows for a direct comparison of each cause of death relative to the amount of attention received in media, policy, and government funding. For example, the ratio between tobacco-related

deaths (440,000 deaths/year) and tobacco-related Media Cloud attention (168,706 occurrences/year) resulted in a relatively high, positive z-score. The ratio of deaths and Media Cloud attention related to poor diet (503,000 deaths/year and 1,103,447 occurrences/year), on the other hand, resulted in a slight, negative z-score. This figure highlights the magnitude of misalignment between media, policies, and government spending, with larger deviations—either positive or negative—indicating more substantial misalignments.

DISCUSSION

Examining the totals for the actual causes of death, as well as the representation in media, legislation, and government funding, helps elucidate public health attention and priorities in
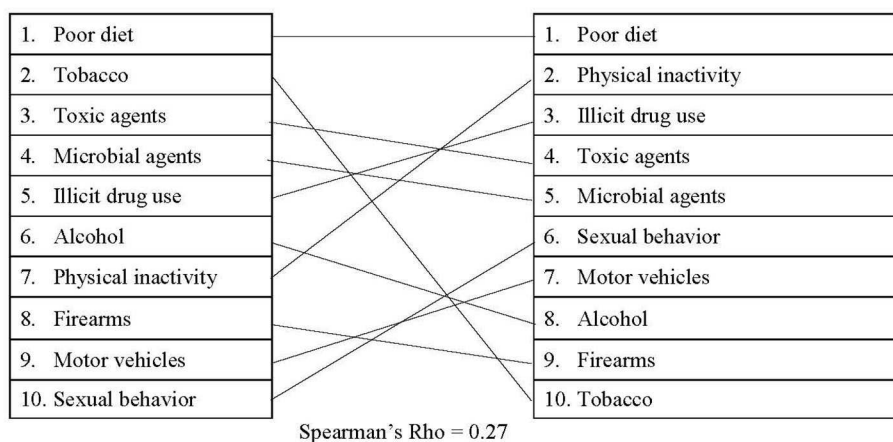
FIGURE 3 | Comparing actual causes of death to proposed legislation.
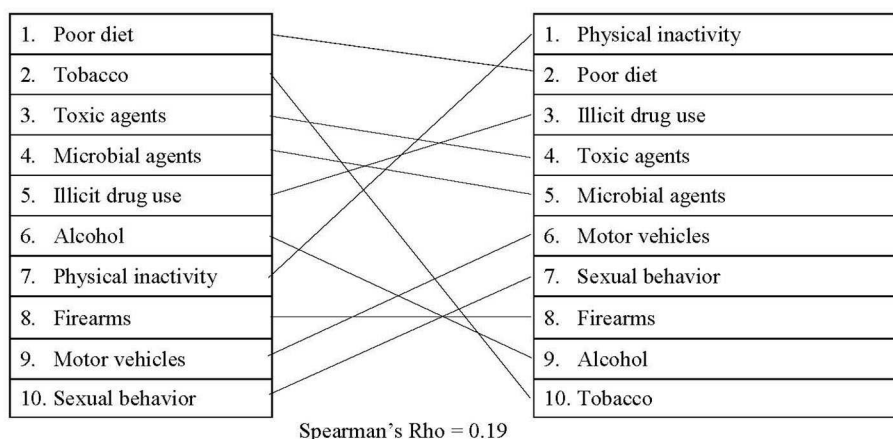
FIGURE 4 | Comparing actual causes of death to passed legislation.

the United States. Overall, our study suggests that the nation's priorities (as measured by media attention, policy attention, and funding) are not consistently aligned with the actual causes of death. Some, such as sexual behavior, receive relatively little media attention, while others, including alcohol, are given little policy consideration. Finally, some causes of death, particularly firearms, are impacted by larger-scale factors. For example, the political ideology and subsequent restrictions surrounding firearms (e.g., the Dickey Amendment) have likely impacted funding streams (38, 39).

Perhaps the largest misalignment is related to tobacco. Though it was ranked as the second largest actual cause of death in the United States, tobacco consistently ranked lower than many other causes of death in media attention, policy legislation, and allocated research funding. This may be due in part to the longstanding knowledge of tobacco's negative health effects, compared to emerging public health issues, such as illicit drug use (in particular opioid use). The consistently low tobacco ranking may also be a result of the strong political influence of the tobacco

industry (40). Finally, the limited presence of tobacco-related focusing events, drivers of policy change that encourage political focus on a particular issue (41, 42), may help to explain the relatively limited emphasis in media, policy, and government spending. Examples of tobacco-related focusing events include the Master Settlement Agreement in 1998, which limited tobacco advertising (43), as well as recent hospitalizations and deaths due to e-cigarette or vaping-associated lung injury (44, 45). Without the presence of such events, chronic diseases may be less likely to find "windows of opportunity" (42) and, consequently, receive media, policy, or funding attention. Overall, these rankings suggest that the resources for some diseases or conditions may be out of proportion with the overall burden (i.e., morbidity and mortality).

Additionally, the Spearman correlations revealed misalignments between the actual causes of death and media, policy, and federal funding. Based on the correlations, legislation may be the most closely aligned with the actual causes of death [proposed: (r_s = 0.27); passed: (r_s = 0.19)]. However, the
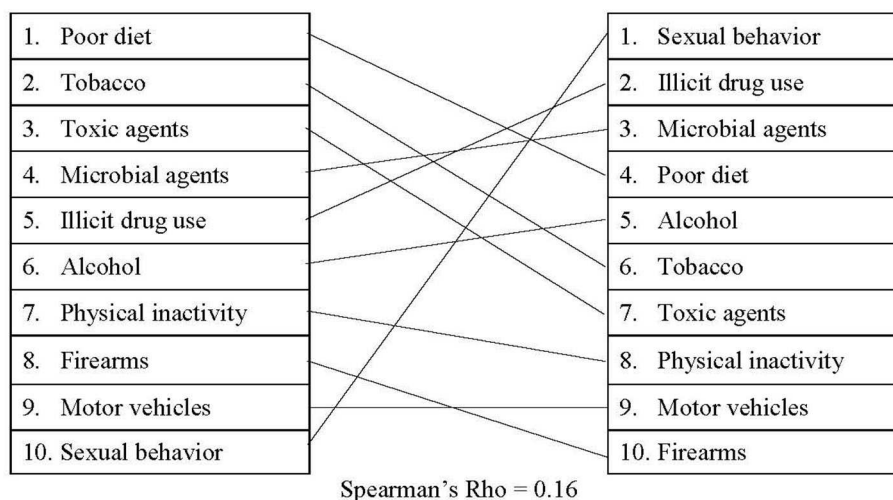
FIGURE 5 | Comparing actual causes of death to government spending.

TABLE 2 | Comparing rank of actual causes of death, media, policy, and funding.

Rank	Actual cause of death	Media presence: Media Cloud	Media presence: Nexis Uni	Policy: #bills proposed	Policy: #bills passed	Government funding
1	Poor diet	Poor diet	Poor diet	Poor diet	Physical inactivity	Sexual behavior
2	Tobacco	Motor vehicles	Motor vehicles	Physical inactivity	Poor diet	Illicit drug use
3	Toxic agents	Firearms	Illicit drug use	Illicit drug use	Illicit drug use	Microbial agents
4	Microbial agents	Illicit drug use	Firearms	Toxic agents	Toxic agents	Poor diet
5	Illicit drug use	Physical inactivity	Physical inactivity	Microbial agents	Microbial agents	Alcohol
6	Alcohol	Microbial agents	Toxic agents	Sexual behavior	Motor vehicles	Tobacco
7	Physical inactivity	Toxic agents	Microbial agents	Motor vehicles	Sexual behavior	Toxic agents
8	Firearms	Alcohol	Tobacco	Alcohol	Firearms	Physical inactivity
9	Motor vehicles	Sexual behavior	Alcohol	Firearms	Alcohol	Motor vehicles
10	Sexual behavior	Tobacco	Sexual behavior	Tobacco	Tobacco	Firearms

correlations between legislation and the actual causes of death are still only small-to-moderate. It is also worth noting that the r-value decreases slightly between proposed legislation and passed legislation. These findings may suggest that lawmakers are attempting to address the actual causes of death but may be encountering difficulties passing legislation. The comparison between Media Cloud and the actual causes of death, on the other hand, revealed a small negative correlation ($r_s = -0.02$), suggesting that this outlet may be the least aligned with the actual causes of death.

Limitation

There are several limitations of our study. First, we acknowledge that mortality is not the only outcome that public health interventions seek to impact but rather is one easily accessible in studies like this one. Though this study selected mortality as its outcome of interest, other factors (e.g., morbidity and socio-political context) also influence the prioritization of public health resources. Another possible limitation of this study relates to the selected databases. For example, while both Media Cloud and

Nexis Uni were chosen to provide an extensive, comprehensive approach to media, these databases do not capture all forms of media attention. As a result, there were likely pertinent data not captured in this analysis, which may have impacted the results. Data identified in this study—in media, policy, and government spending—were analyzed based on quantity, and each occurrence was given an equal weight. Future studies may explore the reach or quality of data from these databases (e.g., placing a relative weight on individual social media shares compared to a national news outlet). It is also important to acknowledge that this paper focused only on the proposal and implementation of federal-level policies. Though state and local-level policies can significantly impact public health outcomes (46), we believe that shifting the nation's focus as a whole will need to include a significant focus at the federal level. Future studies may explore and contrast state and local-level policy and media attention in relation to the actual causes of death. In addition, as noted in previous studies (47), due to the complexity and variation across agencies, as well as difficulty accessing data, we were unable to find public health spending costs for specific
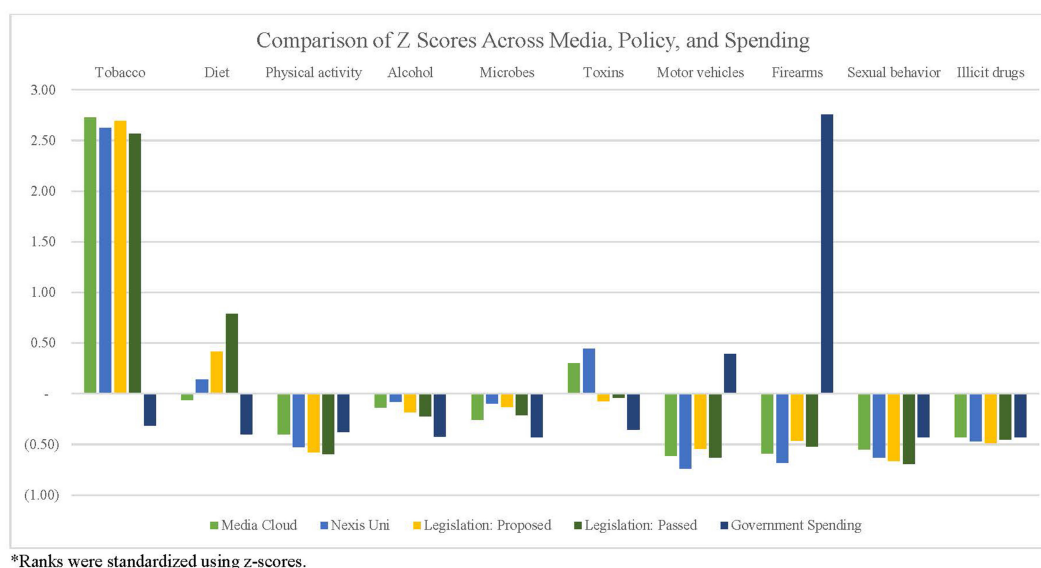
FIGURE 6 | Comparing standardized rank of actual causes of death, media, policy, and funding.

causes of death. As a result, we chose to use the TAGGS database as a proxy for national-level public health spending. Additionally, though we suggest multipronged approaches to address the actual causes of death, we recognize that increased media attention, national policies, and government spending are not causally linked with lower levels of actual causes of deaths. However, as we have described, similar approaches have demonstrated promising results, including decreased morbidity and mortality (29). Lastly, a limitation of this paper was that it did not account for lobbying funds related to specific causes of death. Research has shown that lobbying can impact legislators' voting and, consequently, available funding (46, 48–51). However, analyzing lobbying funds was beyond the scope of this project but could be addressed in future work. Despite these limitations, this study adds to the existing policy literature by exploring media coverage, policy attention, and government spending as indicators of public health attention and priorities in the United States.

Based on the results of their study, McGinnis and Foege called for a greater investment in prevention, thus shifting away from a disease treatment approach (30). Likewise, Mokdad et al. described the substantial number of deaths attributable to poor diet, physical inactivity, and tobacco and suggested that a more preventative approach to health may impact mortality (31). In a related study, Vargas and colleagues found that the leading causes of death in the United States are under-represented in the NIH prevention research portfolio (52). This study revealed similar findings regarding the actual causes of death in the United States. Additionally, it highlighted incongruences between the actual causes of death and media attention, policy attention, and government spending.

There are two primary implications that arise from the findings of this study. First, there is a need be sure that actual causes of death are receiving adequate attention. As previous

researchers have noted, prioritizing the use of limited resources is imperative for public health impact (53). Unfortunately, resources in the United States—media, policy, and funding channels—are currently prioritizing different issues, leading to incongruences in the nation's focus on public health. The misalignments across media, policy, and funding sectors may be related to stakeholders' vested interests (e.g., generating interest in news stories vs. satisfying constituents).

When we consider redistributing limited resources, it is important to clarify that we are not simply advocating for the shifting of resources from one preventable cause of death in favor of another. Public health is often a zero-sum game (i.e., the total amount for prevention is relatively fixed over time), and decreasing mortality rates is far more complex than simply redistributing resources. Instead, we are acknowledging that the actual causes of death would be best addressed through prevention (54), and, unfortunately, resources dedicated to prevention constitute only a small portion of total healthcare spending. In 2017, roughly 95% of healthcare spending was treatment-focused, leaving only 5% for prevention and public health efforts (55). The U.S. healthcare system is primarily focused on medical treatment; however, a shift toward prevention would result in a more effective and efficient use of resources (47). This is particularly challenging in public health, due to the reliance on resource-based planning, which often prioritizes immediate health needs (i.e., medical treatment) over long-term challenges (56). The results of disease prevention efforts may not be immediately apparent, thus diminishing the perceived sense of urgency by stakeholders and the public. Given the limited resources designated for public health efforts, it may be beneficial to maximize the impact of resources to better align with the actual causes of death in the United States. As discussed previously, this approach has demonstrated success in the past (29).

The second implication of this work is the potential benefit of intervening across multiple areas—through media attention, national legislation, and government spending—to impact mortality rates in public health. As we have seen from our approach, coverage in the media does not always correlate with policy and funding action. For example, deaths related to firearms receive a moderate amount of media attention; however, without national-level policy changes and funding increases, the number of annual deaths is unlikely to change. As previous research has suggested, to affect change, we need to intervene at multiple loci of control, involving stakeholders from multiple public health sectors (57). If, for example, media attention, federal policy, and government spending each better addressed tobacco-related deaths—increasing awareness through the media, proposing and passing federal-level legislation, and increasing research surrounding tobacco prevention and cessation—there would be the potential to shift priorities and better address preventable deaths.

Collaboration between researchers and policymakers could be helpful when developing priorities. For example, researchers could strive to more clearly define public health problems and engage in early stages of the policy process; they could also more effectively communicate research findings with both media representatives and policymakers to improve evidence-based policymaking (58–60). We recognize that public health and policy researchers are acting within a broader political, social, and economic context, but these action steps may help address the misalignments between media attention, policy attention, government spending, and the leading actual causes of death. Such coordinated and comprehensive efforts on a national scale could be used to improve health and decrease death totals for many—if not all—of the actual causes of death. However, mobilizing support in these different arenas requires a significant investment, as multilevel priority changes are often difficult undertakings (57). Additionally, we recognize that decentralized government and industry influences on policy in the United States pose a significant barrier to these efforts.

Ultimately, prevention efforts are not a high enough priority in the United States. A national shift toward population-based planning, wherein long-term health outcomes were considered before allocating resources, would encourage a more prevention-centered health system (47). Until then, however, those invested in the nation's health must make the most of the available resources and prioritize public health through media, policy, and government funding.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are publicly available. This data can be found here: 1. Institute for Health Metrics and Evaluation—Available from: http://www.healthdata.org/ 2. Media Cloud—Available from: https://mediacloud.org 3. Nexis Uni—Available from: https://www.lexisnexis.com 4. Congress.gov—Available from: https://www.congress.gov 5. Tracking Accountability in Government Grants Systems—Available from: https://taggs.hhs.gov/.

AUTHOR CONTRIBUTIONS

MP: formal analysis and writing-original draft preparation. AE and SM-R: writing-review and editing. RB: conceptualization, supervision, and writing-review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Leading Causes of Mortality and Prescription Drug Coverage in Canada and New Zealand

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Introduction: Canada may soon see the introduction of a national pharmaceutical insurance system. New Zealand has a government-funded healthcare system used by all residents that operates within a tight cost-containment budget. The objective of this analysis was to compare the main mortality causes in Canada and New Zealand and examine listings in current Canadian provincial public drug plans and the New Zealand national drug formulary.

Materials and Methods: Age-standardized mortality rates from 2000 to 2015 and data on hospital discharges and average length of stay in hospital for Canada and New Zealand were obtained from the Organization for Economic Cooperation and Development's website. Information on insured medications was obtained from Canadian provincial drug plan lists and the New Zealand Pharmaceutical Schedule current in mid-2019.

Results: Hospital discharge rates for cardiovascular disorders, malignancies and respiratory disorders and mortality rates for acute myocardial infarction, ischemic heart disease and cerebrovascular disease were higher, on average over the observation period, in New Zealand than in Canada, but mortality rates for malignancies and respiratory disorders were similar. Reimbursement listing rates for cancer drugs and some cardiovascular medications were lower in New Zealand than in Canada.

Discussion: Higher hospital discharge and mortality rates suggest poorer patient health in New Zealand compared with Canada. This may be due to lower reimbursement listing rates for some medications in New Zealand. New Zealand's drug coverage system has contained costs, but it restricts or denies access to new innovative medicines with the potential to improve patients' lives. Although a New Zealand-style national pharmacare scheme in Canada would offer the opportunity to restrain drug expenditure, it would likely fail to satisfy patients and healthcare providers and could diminish health outcomes, resulting in higher costs in other healthcare sectors.

Keywords: mortality, health outcomes, prescription drugs, Canada, New Zealand, drug insurance

INTRODUCTION

The sustainability of prescription drug insurance coverage is a perennial political issue in Canada. Provincial governments for whom healthcare consumes close to 50% of their overall budgets are concerned about new innovative medications that provide therapies for conditions not previously treatable but have high costs.

The Canadian pharmaceutical environment will soon see significant changes as part of the federal government's focus on "affordability, accessibility and appropriate use of prescription drugs" (1). For example, the government has imposed sweeping changes to the regulations that govern the quasi-judicial tribunal that sets maximum prices for patented medicines sold in Canada (2). The new regulations replace countries that have higher drug prices with lower price countries in the tribunal's international price comparison analysis, enforce a hard, low cost-effectiveness threshold, and impose a reduction in a drug's price if its annual sales exceed a specified amount (3). These changes will reduce Canada's attractiveness to pharmaceutical manufacturers as an important country in which launch their new products (4).

In addition, interest in a national drug insurance program has intensified with the announcement in its 2019 budget that the Liberal federal government is "moving forward" on "foundational elements" of national pharmacare (5). With the re-election of the Liberals in 2019 and support from other like-minded political parties, the process may proceed. Canada is the only country in the world with a universal public health system that covers healthcare providers, hospitalizations and laboratory services but not prescription drugs in the outpatient setting. Reimbursement for drug expenditures is available through government-funded plans and private insurance paid for by individuals or cost-shared with employers or unions. Around two-thirds of Canadians are covered by private insurance, while federal and provincial government drug plans—mainly designed to provide coverage to seniors, social assistance recipients and some special groups, or when costs are deemed to be catastrophic—offer a degree of coverage to about 25% of the population (6, 7). Many private plans provide wider drug coverage than public plans, including brand-name products, but often require deductibles and/or copayments and may have yearly or lifetime financial coverage; in addition, changing employment can lead to a loss of insurance. Government plans have complex systems of deductibles, copayments and premiums and, for many drugs, special or restricted access criteria that results in variation in patient eligibility, out-of-pocket expenses and coverage, which has led to significant inequalities between provinces.

New Zealand has a government-funded universal healthcare system that all residents use. To provide more timely access to medical and dental benefits, about 35% of the adult population has private health insurance most of whom pay for it themselves (8). However, most insurers in the New Zealand market only cover the copayments on prescription medicines that are publicly funded.

New Zealand's government created the Pharmaceutical Management Agency, known as PHARMAC, in 1993 "to make

decisions on which medicines and medical devices are funded in order to get the best health outcomes from within the available funding" (9). PHARMAC operates on a fixed budget for pharmaceuticals so that, when assessing a new medicine for inclusion in the Pharmaceutical Schedule (the drug formulary) (10), funding decisions are based on clinical and economic assessments that examine the need and health benefit of a new medicine and its costs and potential savings (11). Consideration is also given to other drugs that must be forgone and price concessions that must be obtained from manufacturers to fund the new product within the budgetary cycle. PHARMAC takes recommendations from its health technology assessment (HTA) expert committee and negotiates with manufacturers to reach a provisional listing agreement. A product is added to the national Pharmaceutical Schedule only if an acceptable proposal is achieved, which can lead to "bundling" deals with manufacturers for multiple medicines (12). As of June 2019, over 100 medications had been recommended for inclusion in the subsidized program by the HTA committee but were unfunded, some of which had been waiting for funding for more than 10 years (13).

The Canadian federal government's Advisory Council on the Implementation of National Pharmacare examined international models of national pharmacare, including New Zealand's system, but did not recommend that Canada should copy any specific country (14). However, some Canadian health policy analysts have suggested that a Canadian national pharmacare scheme should include some components of the system used to control pharmaceutical costs in New Zealand (15–17). The objective of this evaluation was to review mortality and hospital discharge rates in the three disease areas (malignancies and circulatory and respiratory diseases) that account for more than two-thirds of the deaths in Canada and New Zealand in the light of prescription drug coverage by Canadian provincial public drug plans and the New Zealand national system.

MATERIALS AND METHODS

Mortality data for malignancies and circulatory and respiratory diseases for Canada and New Zealand were obtained from the website of the Organization for Economic Cooperation and Development (OECD) (18) as age-standardized death rates per 100,000 population, standardized to the total OECD population for 2010, for the period between 2000 and 2015 (latest year for which cause of mortality data were available for both countries). Mortality data represent a hard health outcome measure.

Data on hospital discharges, excluding day cases, as a rate per 100,000 population and average length of stay in hospital, calculated by dividing the number of relevant bed-days by the number of discharges during the year, were also obtained for the two countries from 2000 to 2016 (data for both countries were only available for this period) as supplementary information about softer health outcomes.

Information on medications used to treat conditions in the three disease categories covered in Canada was obtained from

TABLE 1 | Comparison of relevant characteristics of the Canadian and New Zealand populations.

	Canada	New Zealand
Population	37 million	4.9 million
Residents living in an urban area (22, 23)	81%	86%
Poverty rate after taxes and transfers (poverty line 60%) in 2014 (18)	0.193	0.196
GINI index in 2018 (24)	31.2	32.5
Indigenous population (25, 26)	4.9% (2016)	15.5% (2018)
Population completing post-secondary education (27, 28)	66% (2017)	79% (2013)
Residents with diabetes in 2017 (29, 30)	7%	6%
Obesity rate in 2017 (18)	26%	32%
Population aged 15+ years smoking daily in 2017 (31, 32)	12%	14%
Liters of alcohol per capita in 2017 (18)	8.1	8.8
Gross domestic product per capita (US$) in 2018 (33)	$46,313	$42,950
Hospital beds per 1,000 population in 2017 (18)	2.6	2.7
Active physicians per 1,000 population in 2017 (18)	2.7	3.0
Nurses per 1,000 population in 2017 (18)	10	10

on-line provincial public drug plan benefit lists current in mid-2019, including any from relevant special or exceptional access product lists maintained by some provinces. Only oncology drug reimbursement information from British Columbia, Alberta, Saskatchewan, Ontario and Quebec was used in the analysis because details of covered cancer drugs are accessible in separate publicly available benefit lists or are included in the provincial formulary for these provinces, whereas the formularies of New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador list some but not all oncology drugs, while the oncology drug formulary for Manitoba is not publicly available. The Pharmaceutical Schedule current at mid-2019 was used to identified relevant subsidized medications, including oncology products, in New Zealand.

Where a medicine was only listed in Canadian formularies, information on regulatory applications approved by the Medicines and Medical Devices Safety Authority (19) was used to ascertain whether the product was approved in New Zealand. Similarly, if a medication was in the New Zealand Pharmaceutical Schedule but not in any Canadian provincial formulary, Health Canada's Drug Product Database (20) was used to determine whether it had regulatory approval in Canada.

Fewer drugs receive regulatory approval in New Zealand (21), which makes comparisons of the comprehensiveness of reimbursement listing challenging. For example, if there are 20 drugs in a class of which only 10 have regulatory approval in New Zealand and all are listed in the Pharmaceutical Schedule, the reimbursement listing rate is 100%. On the other hand, if all 20 drugs have regulatory approval in Canada, but provincial drug plans only cover 10, the reimbursement listing rate is 50%, although the same number of products receive reimbursement in both countries. However, drug reimbursement systems can only include medications that have regulatory approval in their country. Consequently, only reimbursement listing rates (the number of drugs with listing as a percentage of the number with regulatory approval) are reported for each country and compared using Fisher's exact test.

RESULTS

Although large differences exist between the two countries' geographic areas and populations, over 80% of their residents live in an urban area with a similar population density (**Table 1**). Poverty rates in the two countries are similar. Rates of residents with diabetes and obesity or who are regular smokers and the per capita consumption of alcohol, which are risk factors for cardiovascular disease and some cancers, are also similar in the two countries. Both countries have diverse economies, with international trade being a significant component of both economies, although New Zealand has a 7% lower per capita gross domestic product. In addition, both countries provide hospital and physician services without payment at the point of service, with the numbers of hospital beds and active physicians and nurses per 1,000 population in 2017 being virtually the same. These similarities and differences between the two countries should be borne in mind when considering the results of the analysis.

Hospital discharge rates for neoplasms and circulatory diseases in New Zealand between 2000 and 2016 were consistently higher than the rates in Canada by 25% on average, while the rate for respiratory diseases was consistently higher by 67% on average (**Figure 1**). **Figure 2** shows the length of stay in hospital averaged over the 2000–2016 period. Although consistency exists between the two countries in the overall average length of stay and that for respiratory diseases, the New Zealand averages for disorders of the cardiovascular system and heart failure are approximately twice those in Canada and, remarkably, the New Zealand averages for cerebrovascular diseases, ischemic heart disease other than acute myocardial infarction, and hypertensive disease are three to seven times longer than in Canada.

Mortality rates for Canada and New Zealand show that the main causes of death in both countries are malignancies and circulatory and respiratory diseases, accounting for 65.1% of the deaths in Canada and 71.4% of the deaths in New Zealand in

FIGURE 1 | Hospital discharge rate in Canada and New Zealand for neoplasms and circulatory and respiratory diseases, 2000–2016.
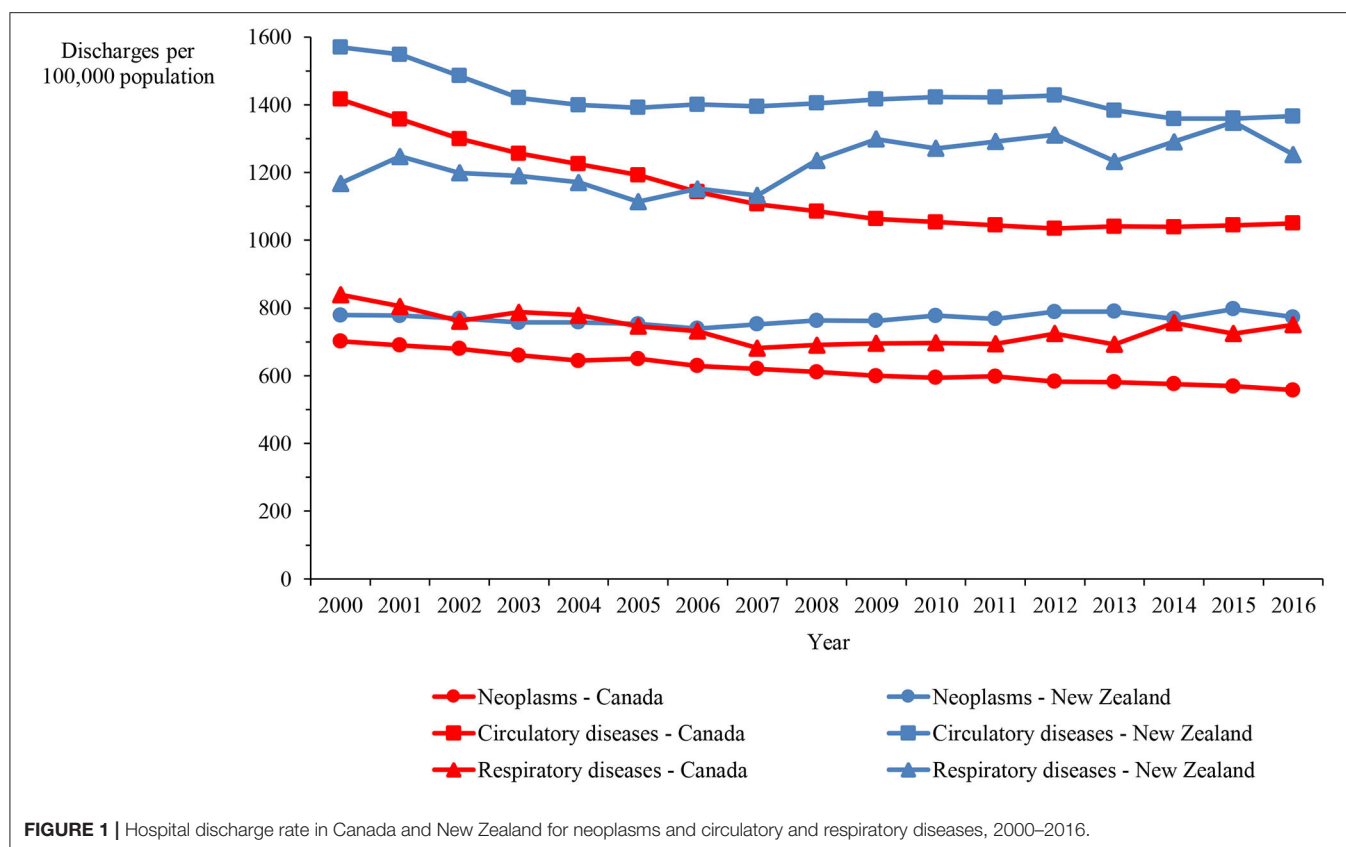
2015. The age-standardized mortality rate for circulatory diseases was higher in New Zealand than Canada by 31.1% on average, ranging between 21.4 and 37.8%, over the 16-year period. In contrast, the rates for malignancies and respiratory diseases were only marginally higher in New Zealand by 2.6% on average (varying between −0.3% and 7.8%) and 5.7% (varying between −9.8% and 15.7%), respectively (**Figure 3**).

Mortality data on ischemic heart disease and cerebrovascular disease, which account for the majority of circulatory disease deaths, demonstrate that, although the rate more than halved in both categories in both countries over the 16-years, the rate in New Zealand exceeded the Canadian rate by 33.6% and 60.9%, on average, for ischemic heart disease and cerebrovascular disease, respectively (**Figure 4**). **Figures 5A,B** show mortality rates for the four major cancers: breast, colorectal, lung and prostate. The New Zealand rate was higher than the Canadian rate for breast, colorectal and prostate cancer by 9.7%, 37.2%, and 32.7% on average, respectively. However, the New Zealand lung cancer rate was lower than the Canadian rate by 27.4%, on average over the 16-year period.

A total of 263 medications from the three system categories (cardiovascular, anti-cancers and respiratory) were identified for which the regulatory approval rate was 85.9% in New Zealand (226 drugs) compared with 97.0% in Canada (255 drugs). Of the medicines with regulatory approval in New Zealand, 127 (56.7%) were listed in the Pharmaceutical Schedule compared with a

median number of 232 drugs (91.0%) with regulatory approval in Canada that are listed in provincial drug plans ($p < 0.0001$).

The overall reimbursement coverage rate in New Zealand was considerably lower than the median listing rate in Canadian provincial drug plans for angiotensin-converting-enzyme inhibitors (ACEIs; 60.0% vs. 100.0%; $p = 0.007$), angiotensin receptor blocking (ARB) drugs (30.8% vs. 100.0%; $p < 0.0001$), statins (71.4% vs. 100.0%; $p = 0.19$), drugs for cancers other than the four major cancer types of breast, colorectal, lung and prostate (56.2% vs. 95.2%; $p = 0.012$), and drugs used to treat multiple types of cancer (75.0% vs. 96.9%; $p = 0.026$) (**Table 2**). The listing rates in the two countries for other cardiovascular drugs and respiratory drugs were reasonably consistent.

DISCUSSION

It has been suggested that a Canadian national pharmacare program should adopt some aspects of the national system used in New Zealand (15–17), making a comparison between the two countries pertinent. While there are, as **Table 1** demonstrates, similarities in several social determinants of health, health care access and factors that are risk factors for cardiovascular disease and some cancers, New Zealand has a higher proportion of indigenous residents, who have poorer levels of education, income and access to health care services. Moreover, New

FIGURE 2 | Average length of hospital stay over 2000–2016 period in Canada and New Zealand for all causes, malignancies, respiratory diseases, and selected cardiovascular conditions.
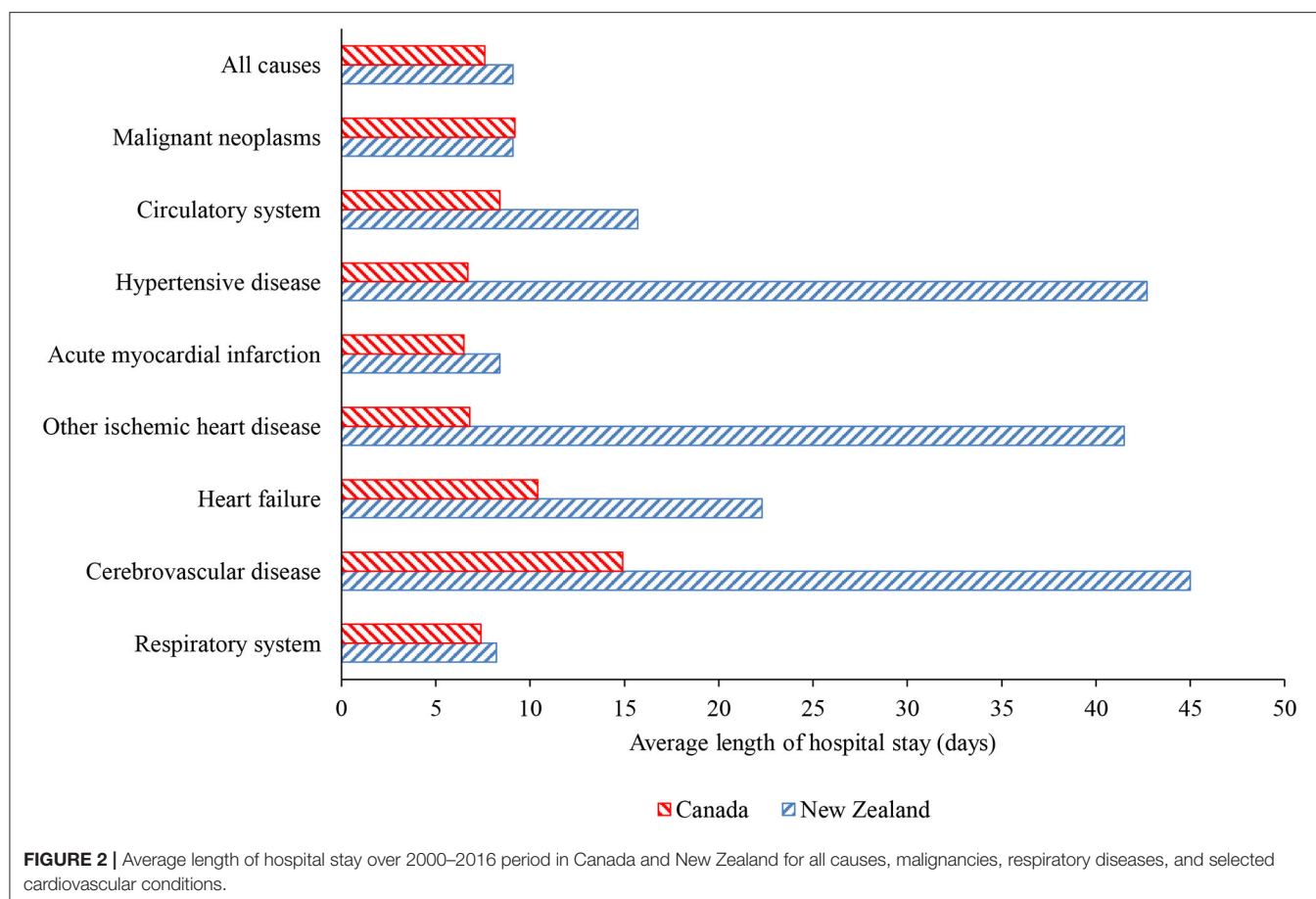
Zealand's much smaller population may make the country a less attractive market to pharmaceutical manufacturers.

Interesting differences in health outcomes can be seen between Canada and New Zealand. In particular, mortality and hospital discharge rates in New Zealand were generally higher and the average length of stay in hospital longer for cardiovascular disorders than in Canada. This is not the result of differences in the prevalence rates of these disorders, which are similar in both countries (34, 35). Nevertheless, increased length of stay may be due to other reasons, such as differences in treatment [e.g., Canadians admitted with acute coronary syndrome may be more likely to receive coronary angiography, which is associated with shorter lengths of stay, than New Zealanders (36)], the type of hospital, or differences in demographic characteristics (37).

Any impact of drug access on cardiovascular mortality is likely to take many years to be seen since many cardiovascular drugs are prescribed for the treatment of conditions such as hypertension and high cholesterol levels, which are risk factors for cardiovascular mortality. A period of 25–30-years is a reasonable length of time to make such an assessment for the ACEI and statin drugs and their impact should be observable by 2015, but the ARB drugs were introduced more recently. However, mortality from ischemic heart and cerebrovascular diseases and the rate of hospital discharges remain higher and

the length of hospital stay for these health conditions is longer in New Zealand compared with Canada. The fewer ACEI and statin drugs and perhaps the ARB drugs funded and available in New Zealand may have contributed to these differences. More drugs in a class may make little difference, but patients are variable biologic entities so that a one-size-fits-all approach does not necessarily work.

Unlike cardiovascular drugs, oncology drugs are not prescribed as preventative therapy but to try to alleviate an existing disorder. Despite the proliferation of cancer therapies over the past 25 years, the lack of oncology drugs in the New Zealand formulary does not appear to have negatively impacted overall cancer mortality. Although mortality from three of the four major cancers (breast, colorectal, and prostate) is higher in New Zealand and fewer drugs specifically targeting these cancers are covered in New Zealand than in Canada, several new oncology drugs approved for marketing are not approved in New Zealand and others have either immature efficacy data or the efficacy results fail to demonstrate an improvement over existing medicines. For four cancers, including breast cancer, PHARMAC staff participated in the development of American Society of Clinical Oncology Cancer Research Committee (ASCO-CRC) targets for clinically meaningful progression-free survival (PFS) and overall survival (OS) and uses them in the evaluation of new drugs (38). For example, trastuzumab emtansine and palbociclib

FIGURE 3 | Mortality in Canada and New Zealand from malignancies and circulatory and respiratory diseases, 2000–2015.
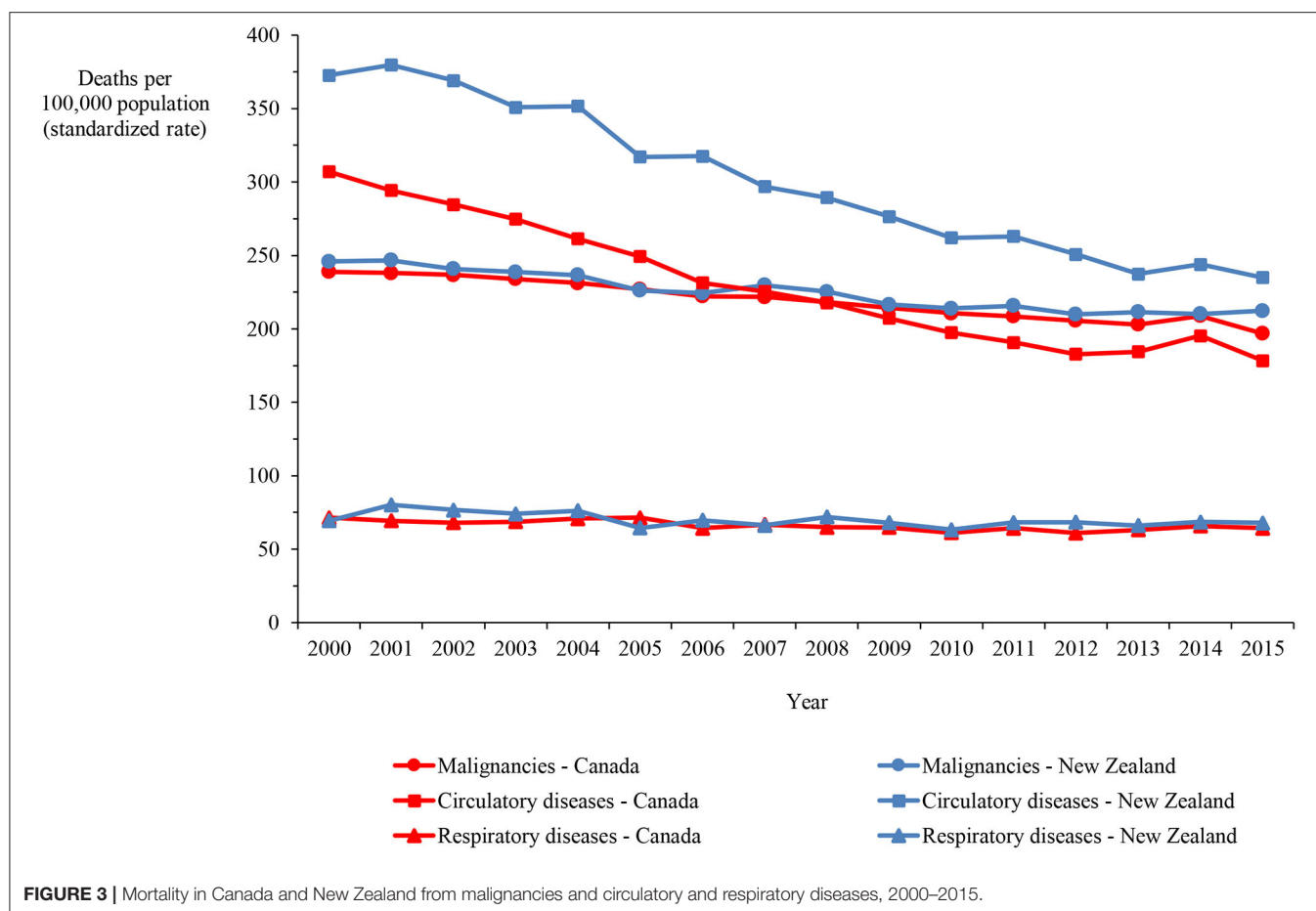
for metastatic breast cancer were not listed in New Zealand at the time of this analysis (although approved for marketing in New Zealand soon after approval in Canada) but were covered by almost all Canadian provincial plans. Trastuzumab emtansine has an improvement in OS and palbociclib has an improvement in PFS in the ASCO-CRC acceptable ranges for clinical value and, after an HTA of more than 2 years, both drugs are now listed in the PHARMAC formulary.

Although mortality rates from lung cancer are higher in Canada in the OECD data for 2000–2015, a recent report comparing survival, mortality and incidence of seven cancers (colon, lung, esophagus, ovary, pancreas, rectum and stomach) in seven countries, including Canada and New Zealand, between 1995 and 2014 demonstrated that the 5-years survival rate for lung cancer in Canada was 40–55% higher between 2000 and 2014 than the New Zealand rate (39). New Zealand had lower survival rates than Canada for all the cancers in the report between 2000 and 2014, except esophageal cancer.

This analysis has limitations. First and foremost, it is an associative assessment so that it is not possible to prove that lower drug listing rates lead to increased mortality and higher hospital discharge rates. Second, despite the OECD data being age-standardized making comparisons valid, other factors may have affected the health outcomes. Third, mortality

rates by cause were only available to 2015 in the OECD data and, consequently, are not current. A further limitation is that listing of medications does not necessarily equate with access. Copayments, deductibles and premiums required by Canadian public drug plans, can place drugs, especially costly new ones, beyond reach. Once a drug is covered in New Zealand, this issue may be less of a problem because, in most cases, patients pay a copayment of only NZ$5 (about CAN$4.50) (40), which is less than half the dispensing fee in most provinces before any copayments or deductibles are added. Clinical criteria for coverage of a drug also frequently restrict access.

No evaluation of the therapeutic value of each drug was performed in this analysis. Some authors have reported that new drugs offer little benefit over existing medicines. For instance, fewer than 50% of the drugs entering the German health care system were reported to add benefit (41)—a re-analysis showed that <40% had minor or "non-quantifiable" benefit (41). Other authors have judged only 10–15% of new drugs to be "therapeutically innovative" (42). However, there is no agreement on the evaluation of therapeutic benefit. Different agencies within and between countries with differing agendas may have conflicting assessments. In some cases, the evaluation

FIGURE 4 | Mortality in Canada and New Zealand for ischemic heart and cerebrovascular diseases, 2000–2015.
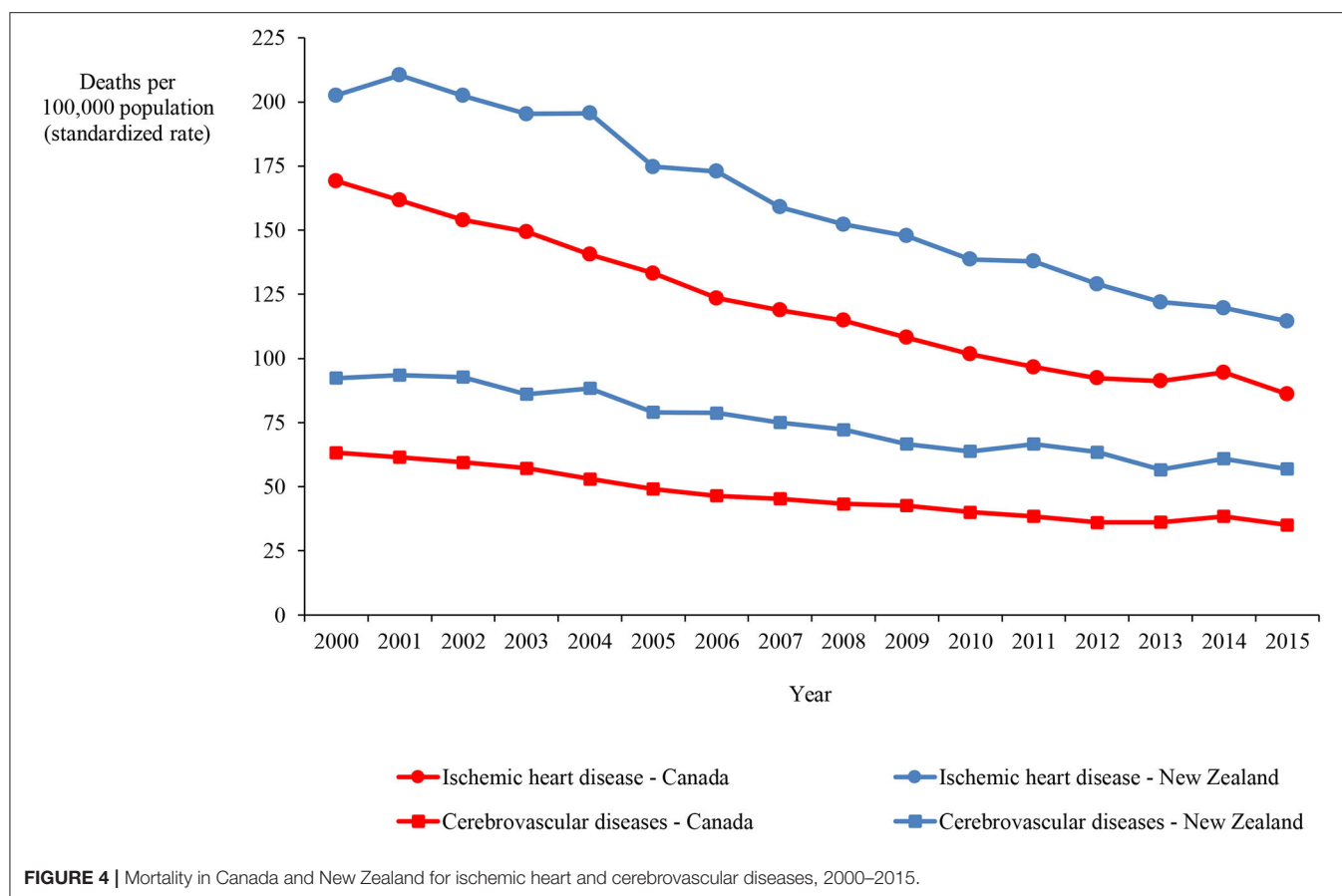
is restricted to meaningful clinical efficacy, while others take a wider perspective and include an assessment of adverse effects and convenience of use (43). Patients frequently take an even broader view about what constitutes therapeutic value.

With 41.8% of new regulatory-approved medications reimbursed in 2011–2016, Canada ranks 18th out of 20 OECD countries, while New Zealand ranks 20th with just 21.8% of new medications reimbursed in the same period (44). Access to new drugs, including anti-hypertensives and statins, has been demonstrated in Canada and several other countries to have a beneficial impact on health outcomes that outweigh the increased cost (45–49), although these findings are not universally accepted (50, 51). The more limited access to anti-hypertensives in New Zealand is surprising because hypertension is "a worldwide problem of enormous consequence" (52). The PHARMAC system has contained costs in New Zealand, but it restricts or denies access to important new medicines with the potential to improve patients' lives.

The attractiveness of a country as a priority jurisdiction in which pharmaceutical companies seek regulatory approval for their new products is based on several factors, such as the potential number of patients with the disorder for which

the drug is indicated, the likelihood of obtaining a profitable price for the product and gaining drug reimbursement coverage, and the country's overall investment climate. The ability to progress innovative treatments through regulatory, reimbursement and pricing processes in a timely manner with government officials and politicians having a comprehensive understanding of costs and system savings (not simply focusing on price) is a critical element. Canada's complex pricing and reimbursement environment already places the country's attractiveness for new innovative medications, especially costly ones, at a lower level than the United States and Europe because innovation is not seen to be valued in Canadian governments' pricing decisions (53). For example, the manufacturer of elexacaftor/tezacaftor/ivacaftor has decided not apply for marketing approval for the drug until the uncertainty surrounding Canada's current regulatory pricing policy is resolved to its satisfaction.

National pharmacare and medication affordability are the current focuses of Canadian politicians, government officials and health policy analysts. Changes in the regulations that govern the tribunal that sets maximum prices for patented medicines sold in Canada (3) will decrease the attractiveness of Canada as a jurisdiction in which global pharmaceutical companies seek regulatory approval for their new products

FIGURE 5 | (A) Mortality in Canada and New Zealand for breast and lung cancers, 2000–2015. **(B)** Mortality in Canada and New Zealand for colorectal and prostate cancers, 2000–2015.
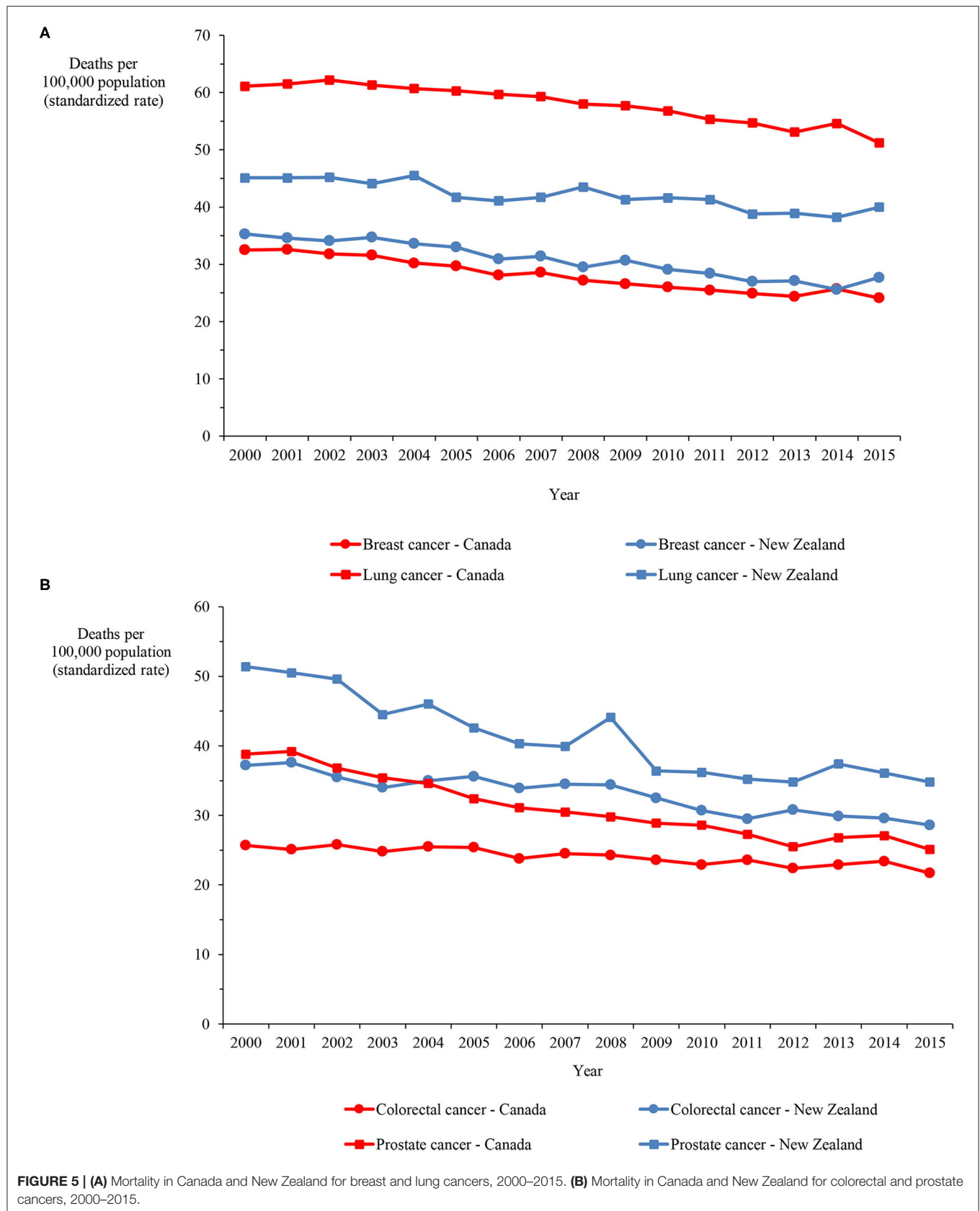
TABLE 2 | Summary results of the comparison of selected drugs approved and listed for benefit in New Zealand and Canada, June 2019.

		New Zealand				Canada			
		Approved for marketing		Listed for benefit in Pharmaceutical Schedule		Approved for marketing		Listed for benefit in provincial drug plans	
Drug group	Available	No.	%	No.	% of Approved	No.	%	Median No. (Range)	% of Approved (Range)
Cardiovascular drugs									
ACEIs*	16	15	93.8	9	60.0	16	100.0	16 (15–16)	100.0 (93.8–100.0)
ARBs*	16	13	81.3	4	30.8	16	100.0	16 (13–16)	100.0 (81.3–100.0)
β-blockers*	14	13	92.9	11	84.6	13	92.9	12 (10–13)	92.3 (76.9–100.0)
Calcium channel blockers	7	7	100.0	6	85.7	6	85.7	6 (5–6)	100.0 (83.3–100.0)
Diuretics	16	14	87.5	12	85.7	13	81.2	12 (9–13)	92.3 (69.2–100.0)
Statins	9	7	77.8	5	71.4	8	88.9	8 (7–8)	100.0 (87.5–100.0)
Other anti-cholesterol	10	7	70.0	7	100.0	9	90.0	7 (5–9)	77.8 (55.6–100.0)
Anti-cancer drugs									
Breast	14	13	92.9	9	69.2	14	100.0	13 (13–13)	92.9 (92.9–92.9)
Colorectal	5	3	60.0	3	100.0	5	100.0	5 (5–5)	100.0 (100.0–100.0)
Leukemia	47	36	76.6	25	69.4	47	100.0	37 (34–41)	78.7 (72.3–87.2)
Lung	8	7	87.5	3	42.9	8	100.0	7 (5–8)	87.5 (62.5–100.0)
Prostate	10	8	80.0	4	50.0	10	100.0	9 (7–10)	90.0 (70.0–100.0)
Multiple cancers	33	32	97.0	24	75.0	32	97.0	31 (30–32)	96.9 (93.8–100.0)
Other cancers	21	16	76.2	9	56.2	21	100.0	20 (18–21)	95.2 (85.7–100.0)
Respiratory drugs									
LABAs[†]	11	10	90.9	9	90.0	11	100.0	11 (10–11)	100.0 (90.9–100.0)
SABAs[†]	3	3	100.0	3	100.0	3	100.0	3 (2–3)	100.0 (66.7–100.0)
Anticholinergics	5	5	100.0	4	80.0	5	100.0	5 (5–5)	100.0 (100.0–100.0)
Steroids	9	9	100.0	8	88.9	9	100.0	9 (6–9)	100.0 (66.7–100.0)
Other COPD drugs	9	8	88.9	6	75.0	9	100.0	6 (3–7)	66.7 (33.3–77.8)

ACEI, Angiotensin-converting-enzyme inhibitor; ARB, Angiotensin receptor blocker; COPD, Chronic obstructive pulmonary disease; LABA, Long-acting beta-agonist; SABA, Short-acting beta-agonist.
*Including in combination with diuretics; [†] Including combinations.

(54, 55). This has the potential to decrease the number of new drugs brought to Canada and, thus, reduce the number covered; early evidence supports this prediction (4, 56). Including tight price controls similar to those used in New Zealand in a national pharmacare scheme in Canada would offer public payers the opportunity to restrain drug expenditure but would likely fail to satisfy patients and healthcare providers and could result in higher costs in other healthcare sectors. More research is required to understand the impact of tighter cost-containment on prescription drug coverage and health outcomes before making radical changes to the Canadian pharmaceutical environment.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. These data can be found here: http://stats.oecd.org/.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Regional Distribution of Causes of Death for Small Areas in Brazil, 1998–2017

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Background: What is the spatial pattern of mortality by cause and sex in Brazil? Even considering the main causes of death, such as neoplasms, cardiovascular diseases, external causes, respiratory diseases, and infectious diseases, there are still important debate regarding the spatial pattern of mortality by causes in Brazil. Evidence shows that there is an overlap in transitional health states, due to the persistence of infectious diseases (e.g., dengue, cholera, malaria, etc.,) in parallel with the increase in chronic degenerative diseases. The main objective of this paper is to analyze the spatio-temporal evolution of three groups of causes of death in Brazil across small areas from 1998 to 2017, by sex.

Methods: We use publicly available data from the System Data Mortality Information (SIM-DATASUS) from 1998 to 2017. We focus on this period due to the better quality of information, in addition to all deaths are registered following the Tenth Revision of the International Classification of Diseases (ICD-10). We estimate standardized mortality rates by sex and cause aggregated into three main groups. We use a ternary color scheme to maximize all the information in a three-dimensional array of compositional data.

Results: We find improvements in mortality from chronic degenerative diseases; faster declines are observed in the Southern regions of the country; but the persistence of high levels of mortality due to infectious diseases remained in the northern parts of the country. We also find impressive differences in external causes of deaths between males and females and an increase in mortality from these causes in the interior part of the country.

Conclusions: This study provides useful information for policy makers in establishing effective measures for the prevention of deaths and public health planning for deaths from external and non-communicable causes. We observed how the distribution of causes of death varies across regions and how the patterns of mortality also vary by gender.

Keywords: mortality, causes of death, ternary color coding, small-areas, micro-regions, Brazil

INTRODUCTION

In the last several decades, Brazil has experienced an accelerated decline in infant, child, and adult mortality (1). The median gain in life expectancy at birth between 1940 and 2015 was about 30 years (2). This change occurred much more quickly than any increase in life expectancy in developed countries over the same period. In 1940, life expectancy at birth in Brazil was around 45.5 years. It reached 67 years in 1990 and 75.5 years in 2015–2020. However, mortality rates observed around 2000 in several regions in the country were like observed rates in the US and Canada in the 1950s, thus showing that there is still room for improvement in terms of life expectancy in the region. In addition, there is wide variation in levels of mortality and life expectancy among and within Latin America countries (3, 4).

Followed by the rapid transition from high to low mortality, Brazil has also experienced a rapid epidemiological transition. However, this last process did not follow the same pattern shown in most industrialized countries and other Latin American countries, such as Chile, Cuba, and Costa Rica (5, 6). Empirical evidence shows that there is an overlap in transitional health states due to high levels of mortality from infectious diseases (e.g., dengue, cholera, malaria, etc.,) in parallel with the increase in mortality from chronic and degenerative diseases (6, 7). Thus, there is no linear path throughout all stages of the epidemiological transition, leaving it in the state of counter-transition (5, 6). In addition, morbidity and mortality are also at high levels, and can be characterized as going through a long-term process of transition and presenting clear regional variation over time. Moreover, there are contrasting epidemiological situations in different regions of the country, creating a scenario of epidemiological polarization (5–7).

However, less is known about the spatial pattern of mortality by cause and sex, even with respect to the main causes of death in Brazil, such as cardiovascular diseases (CVDs), neoplasms, external causes, respiratory diseases, and infectious diseases. Most studies on causes of death have been concentrated on epidemiological and public health aspects, as well as focused on the entire country, large geographic regions, states (federal units) or very specific municipalities (5, 6, 8–15). In summary, Brazil is divided in five major regions (North, Northeast, Southeast, South, and Center-West) comprising 26 states, plus the Federal District, and 5,565 municipalities (according to the 2010 census). These municipalities can be aggregated into 558 micro-regions, although, do not constitute political or administrative entities. Therefore, there is an absence of and a need for studies on variation in mortality over time and space, especially for small areas, although, over the past years there has been an increasing interest in identifying regional differences in mortality within the country for smaller areas (16–19). Policies for public health and well-being must be spatially focused to serve an aging population subject to varying risks of mortality from different causes.

In this paper, we use the approach proposed by Kashnitsky and Schöley (20) to analyze the spatio-temporal evolution of three groups of causes of death in Brazilian micro-regions (small areas) from 1998 to 2017, by sex, in order to answer the following research question: how does the mortality of a micro-region deviate from the Brazilian average? By doing so, we can visualize deviations from the average Brazilian mortality structure and understand how they evolve over time.

Understanding the spatio-temporal heterogeneity of the causes of death in Brazilian micro-regions is important to develop better public health interventions and to explain the variation and differentials in life expectancy at birth in the country, since regional differences are also reflecting differences in other risk factors, such as population age structure, access to health care, quality of hospital care, and variations in risk behavior. This paper contributes to the literature by focusing on small areas of a diverse country and taking space into consideration as an important variable to understand changes in mortality by causes of death.

DATA AND METHODS

Data Source and Level of Analysis

The Brazilian Ministry of Health's database, DATASUS, which is publicly available online (http://www.datasus.gov.br), provides a set of information, such as deaths, causes of death, age, sex, schooling, and race at different geographical levels. Data cleaning and compilation is done at the municipal and state level, and an electronic data file is transferred to the national office every 3 months. The data are available from 1979 and are organized using codes from the International Classification of Diseases Revision (9th from 1980 to 1995 and 10th from 1996 on). For comparability purposes, we use information from 1998 to 2017 (10th Revision). In addition, we decided to work with the most recent data, but also that, at the same time, would provide us a good historical perspective to analyze the spatio-temporal changes. Finally, population by age and sex, at the local level, comes from the Brazilian Censuses (1980, 1991, 2000, and 2010) and intercensal estimates and forecasts from the Brazilian Institute of Geography and Statistics (IBGE).

The original data is available at the municipality level. The main limitation in using city level data in Brazil is that the number and composition of cities change over time. In 1980, there were 3,974 municipalities and, in 2010, there were 5,565. To avoid problems using this information, the municipalities were aggregated into comparable small areas, using the IBGE definition of geographic micro-regions. These micro-regions do not constitute political or administrative entities, they are statistical constructions aggregated using regional, natural, and socioeconomic similarities (21, 22) and their boundaries are constant throughout the research period. That is, we can follow and study 558 small areas in Brazil (**Figure 1**) from 1998 to 2017. Recent papers have used this unit of analysis in their studies on mortality in Brazil (16–18).

The second and most important limitation is the quality of mortality data over time and across regions. Historically, states of the North and Northeast had lower coverage and worse quality of death declarations in relation to the states of the Southeast and South (23–26). However, since the 2000s, there has been an impressive improvement in both coverage and quality (25, 26) although, there are still some limitations with

FIGURE 1 | Brazil by states and micro-regions.

quality of registration in Brazil. Several articles demonstrate that the quality of the information has improved, which allows for adequate comparison among the regions (5, 6, 11, 27, 28). Even so, under-registration of death counts by region was corrected using estimates from Lima and Queiroz (25). One shortcoming is that we use the same adjustment factor for all causes of death.

In this paper, causes of death were grouped into three main groups: chronic degenerative diseases - CDDs (cardiovascular diseases and neoplasm), external causes of death (accidents and homicides), and all other causes (a large part of which is infectious diseases). We focus on these specific causes as they represent most deaths observed in the country (during the period studied, 43.10% of deaths were due to CDDs, 12.50% due to external causes, and 44.40% due to all other causes) and have an interesting variation over the life cycle (5, 6, 29). That is, we investigate deaths that are concentrated at younger ages (0–14 years), adult ages (15–59 years), and older ages (over 60 years).

Data from 1998 to 2017 were grouped into four 5-year periods (1998–2002, 2003–2007, 2008–2012, and 2013–2017) to even out any annual fluctuations. In addition, and to avoid impacts of population age structure on the mortality estimates, we standardize mortality rates using the Brazilian population from

2010, similar approach used by Baptista and Queiroz (17, 18). Thus, estimates of causes of death are capturing only the impacts of different mortality levels by cause over time and across space.

Finally, and before turning to the ternary color coding analysis, we presented descriptive statistics for the three main groups of causes of death by region, sex, and period of analysis. In order to compare the differences across years, we apply *t*-test to determine whether mortality differences, by cause and sex, are statistically different from each other. In our case, the numbers of observations are high enough to perform the analysis. In the analysis, we compare the average mortality for each group of cause to the last period of analysis to identify that they are different over time.

Ternary Color Coding

We used the approach proposed by Kashnitsky and Schöley (20) to investigate the spatio-temporal variation of causes of death in Brazilian micro-regions. The distribution of three groups of causes of death was mapped, rather than showing the proportion of each cause in a separate map, using ternary color coding. According to Schöley (30), this is a technique suitable to the visualization of three part compositions on a surface and that

maximizes the amount of information conveyed by colors. It works by expressing the relative shares among three parts, in our case, three groups of causes of death, as the mixture of three primary colors (we define orange as the primary color for CDDs, cyan for external causes of death, and magenta for all other causes). In other words, ternary color coding is designed to visualize proportions of a whole, that is, anything that splits into three non-negative parts that add up to unity. This is perhaps its biggest limitation of the approach, but theoretically, we can input three different variables, and the results will largely be non-sensical. This is because the ternary color coding will convert these variables to proportions that sum to 1, losing all the information about magnitude; that is, the data points 15, 30, 12, and 30, 60, 24, for example, will be converted into the same proportion, 0.26, 0.53, and 0.21, and thus to the same color.

Another limitation occurs when there is unbalanced data, that is, if there is a concentration of observations in one specific variable. In this study, especially for women, there is a concentration of deaths from chronic degenerative diseases (CDDs) and certain other causes. That is, there is little variation with regards to the visual reference point, which is the greypoint that marks perfectly balanced proportions (30). Therefore, to see the internal variation of the data, the point of reference was changed to the average Brazilian mortality structure, thereby, visualizing direction and magnitude of deviations from that average.

RESULTS

Table 1 presents mean, standard deviation, t-test (to test the differences between the means of two group of causes of death), p-value, and 95% confidence interval for chronic degenerative diseases, external causes, and other causes across states, by sex and over the periods under analysis. The "Obs" column indicates the number of micro-regions in each state. Overall, we observed an increase in the percentage of deaths from CDDs and external causes in the first three periods, with a stabilization in the most recent one. Females have a higher average mortality rate compared to males with respect to the first group of causes, while for external causes the average is ∼3–4 times higher among men. The death rate from CDDs is higher in the South region of the country, while for external causes the Center-West region has the highest averages. In addition, in the analysis, the relationships between the last period (2013–2017) and the others were statistically significant in all situations, indicating the null hypothesis (that the means are equal – using t-test) can be rejected.

Figure 2 (males) and **Figure 3** (females) show the proportional distribution of groups of causes of death across Brazilian micro-regions in the four 5-year periods studied. Before presenting the main findings, we show an example to interpret the ternary color coding. For this, we use males (**Figure 2**) for the period 1998–2002 (top left) as an example. Each point within the triangle represents a micro-region. The reading on the percentage observed in each group of causes of death and micro-region occurs in a clockwise direction. Therefore, in

this study, the percentage of CDDs can be read on the left side of the triangle, external causes on the right side, and all other causes at the bottom. Taking the visual reference point (point of intersection of the three lines within the triangle) as an example, which is the average Brazilian mortality structure, the observed percentages are 34.2, 14.6, and 51.2 for CDDs, external causes, and all other causes, respectively. The darker the color of a micro-region, the higher the share of deaths observed for that group of causes. On the other hand, the grayer a micro-region is, the more balanced the three proportions are.

Regarding the overall results, they indicate that, when comparing males and females, the percentage of deaths due to the groups of CDDs, and other causes is higher for females in all periods and states, while the percentage of deaths due to external causes is higher for males. In addition, results confirm that the ternary compositions are much clearer and more spread out for men, since the data are more balanced.

External causes represent the largest percentage difference between the sexes. Only the state of São Paulo, the most developed state in the country, has a percentage difference of <10 in all periods. The state of Rio Grande do Sul slightly exceeds this percentage in the last period of analysis. At the other end, the percentage difference in Roraima is ∼20% greater for males, although, it shows a slight decline in the period 2013–2017. For males, external causes of death increased very rapidly since the 1980's, having negative impacts on the variation and evolution of life expectancy in Brazil and increasing the gender gap. In addition, there are important changes in the spatial distribution over time.

As for the spatio-temporal variation, and taking into account the visual reference point, **Figures 2**, **3** show that the average Brazilian mortality structure showed very similar changes of intensity for both sexes over the years, although the changes were quite different proportionally. Roughly speaking, CDDs increased significantly from 1998–2002 to 2003–2007 and then "stabilized" (proportionately) in the following years. Meanwhile, external causes remained constant in the first two periods and rapidly increased from 2003–2007 to 2008–2012, with the last period being similar to the previous one. Finally, other causes showed a significant drop between the first two periods and a less intense drop between 2003–2007 and 2008–2012, with the last period (2013–2017) also stable in relation to the previous one.

A more specific analysis of the spatio-temporal variation by sex shows that for males (**Figure 2**), the micro-regions of the North and Northeast, less developed and poorest regions of the country, have shown a reduction in the proportion of deaths from other causes over the years, particularly the micro-regions of the states of Acre, Amazonas, and Pará (North) and Maranhão, Piauí, Paraíba, Alagoas, Sergipe, and Bahia (Northeast), while an increase in the proportion of deaths from CDDs is observed. This combination reflects a narrowing gap between these regions and the average Brazilian mortality structure. In the Center-West, Southeast, and South regions, the proportion of CDDs increased between 1998–2002 and 2003–2007 in all states but declined in the following years. Meanwhile, other diseases made the reverse movement. In summary, the mortality structure observed in the states that are

TABLE 1 | Descriptive statistics – chronic degenerative, external causes, and other causes, by sex and period.

	State	Obs	(Mean; Std. Dev.) 1998–2002			(Mean; Std. Dev.) 2003–2007			(Mean; Std. Dev.) 2008–2012			(Mean; Std. Dev.) 2013–2017			t-statistic	p-value	95% CI
			Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes			
Males	Rondônia	8	35.51; 4.37	22.71; 3.46	41.78; 3.28	38.05; 1.97	21.30; 3.68	40.66; 2.46	38.54; 2.52	22.62; 4.10	38.84; 2.94	39.52; 2.50	20.94; 1.92	39.54; 2.77			
	Acre	5	24.04; 7.69	11.10; 4.89	64.86; 11.21	34.20; 3.12	12.08; 3.53	53.71; 4.12	34.02; 2.36	16.63; 1.05	49.35; 3.25	38.53; 4.19	18.67; 1.94	42.79; 2.36			
	Amazonas	13	25.79; 5.87	14.28; 6.25	59.94; 8.22	26.60; 6.26	13.25; 4.93	60.15; 9.82	29.51; 5.92	17.26; 5.23	53.22; 7.95	36.28; 4.80	17.34; 3.95	46.37; 4.53			
	Roraima	4	30.75; 5.92	30.58; 3.31	38.67; 6.00	35.65; 8.09	25.80; 2.92	38.56; 7.20	34.40; 5.17	28.10; 4.57	37.50; 4.19	36.94; 3.94	25.49; 4.00	37.57; 4.36			
	Pará	22	22.70; 7.71	14.03; 7.22	63.27; 11.94	27.96; 5.74	16.83; 8.16	55.21; 10.30	32.70; 4.41	20.73; 7.28	46.57; 7.95	36.05; 3.15	21.44; 5.06	42.52; 4.54			
	Amapá	4	24.33; 9.24	22.04; 5.34	53.63; 7.98	27.71; 4.32	21.73; 3.33	50.56; 5.92	27.39; 8.01	24.73; 4.16	47.88; 4.60	32.50; 5.17	23.22; 5.15	44.27; 1.02			
	Tocantins	8	33.03; 6.05	17.22; 3.49	49.75; 9.26	46.13; 2.17	19.00; 2.05	34.87; 2.50	41.90; 2.67	22.86; 1.65	35.23; 2.64	41.60; 2.63	24.35; 2.18	34.05; 1.98			
	Maranhão	21	22.89; 6.94	11.16; 3.83	65.95; 8.40	34.34; 7.66	13.75; 2.83	51.91; 8.35	41.63; 3.00	19.04; 3.37	39.33; 4.12	41.79; 2.82	19.72; 2.88	38.48; 2.27			
	Piauí	15	31.59; 6.08	11.05; 1.98	57.36; 7.32	38.78; 4.08	14.69; 1.73	46.53; 4.37	44.95; 3.30	19.80; 2.35	35.26; 3.81	44.65; 2.64	18.49; 1.79	36.86; 3.68			
	Ceará	33	31.46; 4.89	17.06; 2.47	51.48; 4.60	37.01; 2.94	19.66; 2.62	43.33; 3.73	39.95; 2.57	23.27; 3.08	36.78; 3.83	39.43; 2.72	23.42; 3.58	37.15; 3.62			
	Rio Grande do Norte	19	26.03; 6.71	16.51; 2.49	57.46; 7.13	37.81; 3.28	18.67; 3.70	43.51; 2.64	41.82; 2.92	20.49; 3.58	37.69; 2.86	39.54; 3.44	21.86; 3.45	38.60; 2.56			
	Paraíba	23	18.15; 5.01	10.22; 3.21	71.63; 7.20	35.18; 5.41	14.46; 2.76	50.36; 5.95	39.74; 2.73	19.05; 2.80	41.21; 3.78	39.21; 2.27	19.46; 1.95	41.33; 2.69			
	Pernambuco	19	27.84; 12.08	19.49; 3.87	52.67; 10.62	35.47; 6.46	20.66; 1.89	43.88; 5.88	39.78; 7.96	20.40; 4.33	39.81; 4.49	38.05; 3.20	19.35; 3.42	42.59; 5.70			
	Alagoas	13	20.97; 5.93	15.56; 2.40	63.47; 6.00	31.61; 3.72	20.30; 1.95	48.09; 3.77	35.00; 3.98	24.62; 2.66	40.39; 3.49	37.12; 2.78	22.40; 1.44	40.48; 2.47			
	Sergipe	13	21.02; 4.76	16.79; 2.97	62.20; 5.93	35.05; 2.58	18.50; 1.99	46.45; 2.37	36.38; 2.01	21.27; 2.44	42.35; 2.23	34.00; 1.80	22.77; 2.57	43.23; 2.26			
	Bahia	32	25.06; 6.40	13.55; 3.23	61.39; 7.80	29.50; 4.84	15.31; 3.36	55.20; 6.10	32.58; 4.14	20.59; 3.46	46.82; 4.90	32.99; 4.07	21.00; 2.84	46.01; 4.60			
	Minas Gerais	66	36.93; 7.42	10.30; 2.13	52.77; 7.97	39.67; 7.34	12.11; 2.68	48.22; 6.95	38.47; 5.36	15.22; 2.80	46.31; 5.35	38.24; 4.20	16.74; 3.22	45.03; 3.70			
	Espírito Santo	13	37.04; 4.20	17.83; 3.05	45.13; 5.45	45.89; 3.88	19.53; 2.82	34.58; 3.66	43.61; 2.43	24.51; 2.77	31.88; 1.95	42.76; 2.92	23.82; 2.59	33.42; 2.12			
	Rio de Janeiro	18	43.67; 4.70	16.40; 4.21	39.93; 2.90	44.96; 4.99	16.07; 4.14	38.97; 3.02	43.69; 3.38	16.68; 3.24	39.64; 2.04	42.70; 3.58	17.01; 3.08	40.29; 2.04			
	São Paulo	63	42.34; 4.68	14.08; 3.06	43.58; 5.14	43.18; 4.78	12.77; 1.89	44.05; 4.84	41.80; 4.49	12.96; 1.69	45.24; 4.56	42.58; 4.16	12.42; 1.51	45.00; 4.22			
	Paraná	39	47.36; 4.70	14.37; 2.23	38.27; 4.10	48.01; 3.62	15.49; 2.72	36.50; 3.57	44.27; 3.51	18.67; 2.68	37.05; 3.36	43.70; 2.53	18.55; 2.30	37.75; 2.72			
	Santa Catarina	20	44.02; 3.76	13.93; 1.64	42.05; 3.53	45.99; 3.97	14.87; 1.51	39.14; 3.51	46.02; 3.57	16.32; 2.14	37.66; 3.26	45.74; 3.38	16.41; 1.95	37.86; 3.21			
	Rio Grande do Sul	35	48.59; 2.80	12.77; 1.90	38.64; 2.96	48.89; 2.57	13.02; 2.05	38.08; 2.37	47.29; 2.76	14.77; 2.35	37.95; 1.95	45.71; 3.01	15.84; 2.45	38.44; 2.38			
	Mato Grosso do Sul	11	43.42; 3.80	17.46; 2.26	39.12; 4.86	47.56; 2.39	17.77; 1.89	34.67; 3.53	44.42; 1.85	19.97; 3.16	35.61; 3.03	43.74; 1.99	18.63; 2.73	37.64; 3.17			
	Mato Grosso	22	40.80; 3.78	21.97; 3.95	37.22; 5.11	42.79; 3.47	20.36; 2.97	36.86; 3.37	38.50; 2.76	22.89; 2.66	38.61; 4.10	35.83; 3.42	23.05; 2.64	41.12; 3.77			
	Goiás	18	37.35; 3.99	17.69; 2.30	44.97; 4.14	40.13; 3.91	16.88; 2.11	42.99; 3.58	39.00; 1.96	19.62; 2.48	41.39; 2.27	38.73; 1.84	22.49; 2.29	38.78; 1.76			
	Distrito Federal	1	46.35; NA	17.10; NA	36.56; NA	49.50; NA	16.19; NA	34.30; NA	45.91; NA	19.69; NA	34.40; NA	45.23; NA	18.12; NA	36.65; NA			
	Overall	558	34.77; 10.87	14.71; 4.71	50.53; 11.92	39.57; 7.89	15.80; 4.28	44.63; 8.28	40.10; 5.89	18.60; 4.69	41.29; 6.20	40.05; 4.89	18.90; 4.39	41.05; 4.87			
	1998–2002 vs. 2013–2017																
	Chronic degenerative														−13.59	<2e−16 ***	[−6.05––4.52]
	External causes														−22.03	<2e−16 ***	[−4.56––3.82]
	Other causes														19.51	1.33e−12 ***	[8.52–10.43]
	2003–2007 vs. 2013–2017																
	Chronic degenerative														−1.98	<2e−16 ***	[−0.97––0.004]
	External causes														−21.76	<2e−16 ***	[−3.38––2.82]

(Continued)

TABLE 1 | Continued

State		Obs	(Mean; Std. Dev.) 1998–2002			(Mean; Std. Dev.) 2003–2007			(Mean; Std. Dev.) 2008–2012			(Mean; Std. Dev.) 2013–2017			t-statistic	p-value	95% CI
			Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes			
	Other causes														12.49	<2e−16 ***	[3.02–4.15]
2008–2012 vs. 2013–2017																	
	Chronic degenerative														0.31	<2e−16 ***	[−0.25–0.35]
	External causes														−2.97	<2e−16 ***	[−0.49–0.10]
	Other causes														1.55	<2e−16 ***	[−0.07–0.56]
Females Rondônia		8	44.17; 2.87	5.43; 1.21	50.40; 2.36	47.02; 2.98	5.43; 0.71	47.54; 2.46	46.61; 2.76	6.31; 0.86	47.09; 3.13	46.36; 3.05	5.75; 0.73	47.89; 3.06			
Acre		5	28.35; 7.07	3.63; 1.82	68.02; 8.84	40.12; 1.04	3.13; 1.01	56.75; 1.54	40.20; 2.15	4.40; 0.69	55.41; 2.49	44.93; 3.35	4.21; 0.38	50.86; 3.26			
Amazonas		13	29.50; 9.14	3.65; 3.20	66.85; 10.78	31.41; 6.51	3.24; 1.19	65.35; 6.19	35.16; 6.43	4.39; 1.98	60.45; 6.80	42.71; 6.30	3.60; 1.71	53.69; 5.01			
Roraima		4	35.38; 9.34	7.43; 1.72	57.19; 9.04	42.62; 8.73	5.82; 0.68	51.56; 8.75	46.53; 8.57	7.87; 1.09	45.60; 8.03	39.97; 4.47	8.08; 1.61	51.95; 3.55			
Pará		22	27.25; 10.14	3.24; 1.70	69.50; 11.05	34.99; 8.91	3.70; 1.71	61.30; 10.0	41.45; 5.62	4.33; 2.30	54.22; 6.50	44.05; 3.59	4.51; 1.04	51.45; 3.62			
Amapá		4	28.51; 12.71	2.74; 2.04	68.76; 13.28	31.31; 9.78	5.71; 2.28	62.97; 8.32	37.13; 4.28	6.58; 1.75	56.29; 4.54	37.91; 7.74	5.02; 2.13	57.07; 8.21			
Tocantins		8	40.70; 7.91	4.96; 1.27	54.34; 8.99	56.25; 2.52	4.86; 0.65	38.89; 2.67	51.86; 2.03	6.59; 0.87	41.55; 2.38	50.84; 3.64	6.78; 1.12	42.38; 2.85			
Maranhão		21	25.82; 8.33	3.09; 1.09	71.09; 8.97	40.36; 8.57	3.63; 0.71	56.00; 8.76	51.54; 3.29	4.47; 1.04	43.99; 3.60	50.81; 2.25	4.78; 0.86	44.41; 2.18			
Piauí		15	33.18; 7.92	2.97; 0.91	63.85; 8.14	46.10; 5.78	3.47; 0.57	50.42; 5.73	53.50; 4.01	5.18; 0.97	41.31; 4.18	52.75; 4.46	4.90; 0.72	42.35; 4.72			
Ceará		33	39.11; 5.43	3.92; 0.78	56.97; 5.44	47.24; 4.06	3.89; 0.59	48.87; 4.20	52.73; 3.70	4.67; 0.92	42.59; 3.82	50.28; 3.51	4.71; 0.90	45.02; 3.79			
Rio Grande do Norte		19	30.57; 7.72	3.75; 0.73	65.68; 7.74	45.80; 3.11	3.86; 0.53	50.34; 3.13	52.40; 3.13	4.52; 0.86	43.09; 3.14	48.85; 2.66	4.54; 0.88	46.61; 2.58			
Paraíba		23	21.25; 5.80	2.12; 0.68	76.63; 6.04	42.27; 6.93	2.90; 0.62	54.84; 7.10	49.70; 3.49	3.92; 0.84	46.38; 3.52	47.85; 2.65	4.02; 0.75	48.14; 2.98			
Pernambuco		19	32.52; 10.70	3.45; 1.06	64.03; 10.97	42.70; 12.74	3.60; 1.09	53.70; 13.40	50.86; 8.99	4.41; 1.29	44.73; 8.10	49.68; 12.31	4.08; 1.22	46.24; 11.39			
Alagoas		13	25.56; 6.91	2.94; 0.56	71.50; 6.93	40.35; 4.69	3.62; 0.63	56.03; 4.70	46.16; 4.14	4.28; 1.03	49.56; 3.96	47.86; 2.87	4.07; 0.66	48.07; 2.74			
Sergipe		13	26.14; 6.95	3.57; 0.86	70.30; 7.08	45.57; 2.63	3.86; 0.75	50.57; 2.81	48.94; 2.72	5.19; 0.84	45.87; 2.60	45.82; 2.52	5.68; 1.11	48.49; 2.57			
Bahia		32	28.46; 8.66	3.55; 0.92	67.99; 9.25	35.96; 6.17	3.88; 0.84	60.16; 6.45	41.50; 5.18	4.89; 0.79	53.60; 5.46	41.28; 4.55	4.90; 0.81	53.82; 4.62			
Minas Gerais		66	42.38; 8.11	3.38; 0.79	54.25; 8.30	44.97; 7.27	3.62; 0.80	51.41; 7.24	44.91; 5.12	4.76; 0.84	50.33; 5.16	44.10; 3.62	5.09; 0.89	50.81; 3.74			
Espírito Santo		13	42.26; 5.56	5.02; 0.83	52.72; 5.74	52.43; 4.50	5.83; 0.93	41.74; 4.28	52.66; 2.31	7.47; 0.86	39.87; 2.68	49.16; 1.76	8.04; 1.02	42.81; 1.88			
Rio de Janeiro		18	50.55; 3.78	4.68; 1.03	44.77; 3.39	50.47; 3.60	4.55; 0.97	44.98; 3.51	48.57; 2.98	5.61; 1.35	45.82; 2.92	46.47; 3.33	5.50; 0.85	48.04; 3.13			
São Paulo		63	49.78; 5.08	4.24; 0.69	45.98; 5.08	48.81; 4.82	3.93; 0.69	47.26; 4.93	46.78; 4.55	4.25; 0.75	48.96; 4.61	45.81; 4.29	4.43; 0.97	49.76; 4.17			
Paraná		39	54.50; 4.46	4.11; 0.85	41.40; 4.67	54.57; 4.03	4.36; 0.82	41.07; 4.20	51.57; 3.26	5.43; 1.09	43.00; 3.30	50.04; 2.85	5.59; 1.02	44.36; 2.88			
Santa Catarina		20	49.92; 4.35	4.59; 0.82	45.49; 4.42	51.33; 4.19	4.65; 0.72	44.02; 4.12	51.22; 3.62	5.28; 1.15	43.50; 3.65	50.59; 3.54	5.79; 1.12	43.61; 3.53			
Rio Grande do Sul		35	56.36; 3.20	4.05; 0.71	39.59; 3.26	56.23; 2.60	4.10; 0.80	39.67; 2.70	53.40; 2.43	4.89; 1.17	41.71; 2.33	51.26; 2.75	5.43; 1.31	43.30; 2.79			
Mato Grosso do Sul		11	51.83; 4.18	5.22; 0.70	42.95; 4.46	55.05; 2.85	5.27; 1.22	39.68; 3.14	51.00; 2.42	6.74; 1.27	42.25; 2.71	48.80; 1.94	6.86; 1.61	44.34; 2.81			
Mato Grosso		22	51.14; 4.96	6.19; 1.38	42.67; 5.35	51.56; 2.63	5.75; 1.57	42.69; 2.80	47.31; 3.17	6.75; 1.36	45.94; 3.68	44.27; 2.81	6.49; 1.01	49.23; 3.31			

(Continued)

TABLE 1 | Continued

State		Obs	(Mean; Std. Dev.) 1998–2002			(Mean; Std. Dev.) 2003–2007			(Mean; Std. Dev.) 2008–2012			(Mean; Std. Dev.) 2013–2017			t-statistic	p-value	95% CI
			Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes	Chronic degenerative	External causes	Other causes			
Goiás		18	45.74; 4.64	5.33; 0.50	48.94; 4.89	47.88; 3.82	5.02; 0.63	47.10; 3.83	46.59; 2.30	6.15; 0.68	47.25; 2.41	46.21; 2.49	7.22; 0.85	46.57; 2.77			
Distrito Federal		1	55.06; NA	5.11; NA	39.84; NA	55.21; NA	5.57; NA	39.22; NA	53.70; NA	6.28; NA	40.02; NA	51.96; NA	6.22; NA	41.82; NA			
Overall		558	40.72; 12.62	3.96; 1.36	55.32; 13.27	46.47; 8.51	4.10; 1.12	49.43; 8.89	48.13; 6.02	5.03; 1.38	46.84; 6.24	47.12; 5.17	5.17; 1.38	47.71; 5.25			
1998–2002 vs. 2013–2017																	
	Chronic degenerative														−12.01	5.13e−07 ***	[−7.44−−5.35]
	External causes														−20.65	<2e−16 ***	[−1.32−−1.09]
	Other causes														13.97	4.08e−11 ***	[6.54–8.67]
2003–2007 vs. 2013–2017																	
	Chronic degenerative														−1.85	<2e−16 ***	[−1.32–0.04]
	External causes														−22.60	<2e−16 ***	[−1.17−−0.98]
	Other causes														4.96	<2e−16 ***	[1.04–2.40]
2008–2012 vs. 2013–2017																	
	Chronic degenerative														6.24	<2e−16 ***	[0.69–1.33]
	External causes														−3.07	<2e−16 ***	[−0.22−−0.05]
	Other causes														−5.34	<2e−16 ***	[−1.20−−0.55]

Signif. codes: *p≤ 0.05; **p≤0.01; ***p≤ 0.001.

FIGURE 2 | Distribution of groups of causes of death by micro-regions, males, Brazil - time series 1998–2002 (top left), 2003–2007 (top right), 2008–2012 (bottom left), and 2013–2017 (bottom right).
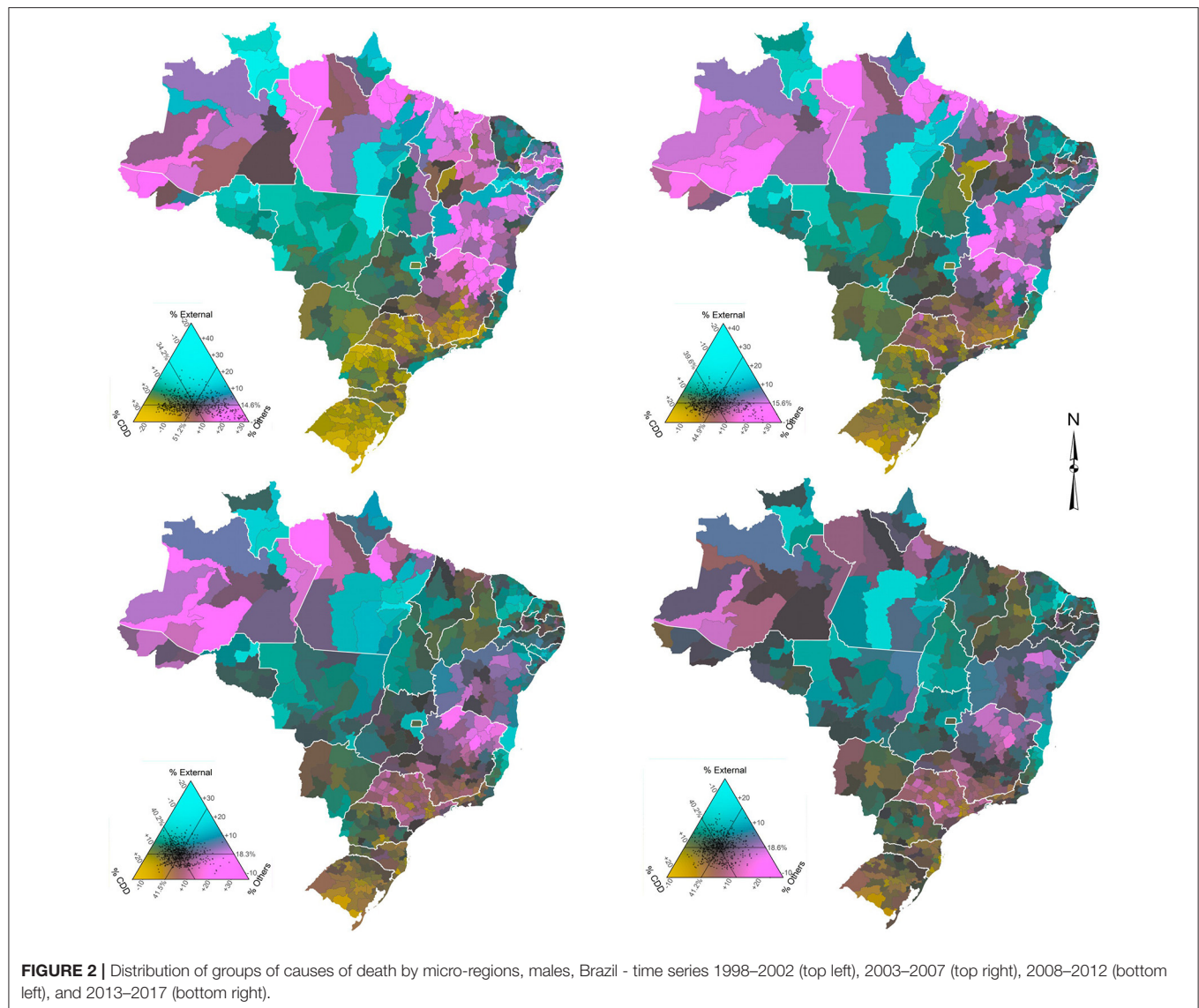
closest to the average Brazilian mortality structure for men are Tocantins (North) and Ceará (Northeast) - 1998–2002; Piauí (Northeast) - 2003–2007; Maranhão and Paraíba (Northeast) and Goiás (Center-West) - 2008–2012; and Maranhão and Paraíba (Northeast) - 2013–2017.

Regarding females (**Figure 3**), the first observation concerns the low percentage and small temporal variation in deaths from external causes registered in most micro-regions, which demonstrates how highly unbalanced the data are. This also makes the averages of micro-regions closer to the national average. The states with the highest percentages of deaths from external causes are Roraima (North), Espírito Santo (Southeast), and Mato Grosso (Center-West), while the lowest percentage is observed in the state of Paraíba (Northeast). As the weight of external causes is much lower in the mortality of women compared to men, the percentages of CDDs and other causes acquire additional importance, although, the spatio-temporal

configuration is often like those observed in men. The Northern and Northeastern micro-regions showed a significant increase in the proportion of deaths from CDDs between 1998 and 2012 (first three periods), while the same intensity was observed in the reduction of deaths from other causes in the period. However, in the last period (2013–2017), the process was reversed in most states in these regions, although, to a much lesser intensity. That is, there was an increase in the proportion of deaths from other diseases and a decrease in the proportion of deaths from CDDs. In the micro-regions of the Center-West, Southeast, and South, in general, a small increase in the proportion of deaths from CDDs and a decrease in deaths from other causes between 1998–2002 and 2003–2007 was observed. However, in the following years the movement was reversed. Specifically, the state of Minas Gerais (Southeast) draws attention, particularly the micro-regions of the north/northeast of the state, where there was a drop in the proportion of deaths from other causes and

FIGURE 3 | Distribution of groups of causes of death by micro-regions, females, Brazil - time series 1998–2002 (top left), 2003–2007 (top right), 2008–2012 (bottom left), and 2013–2017 (bottom right).
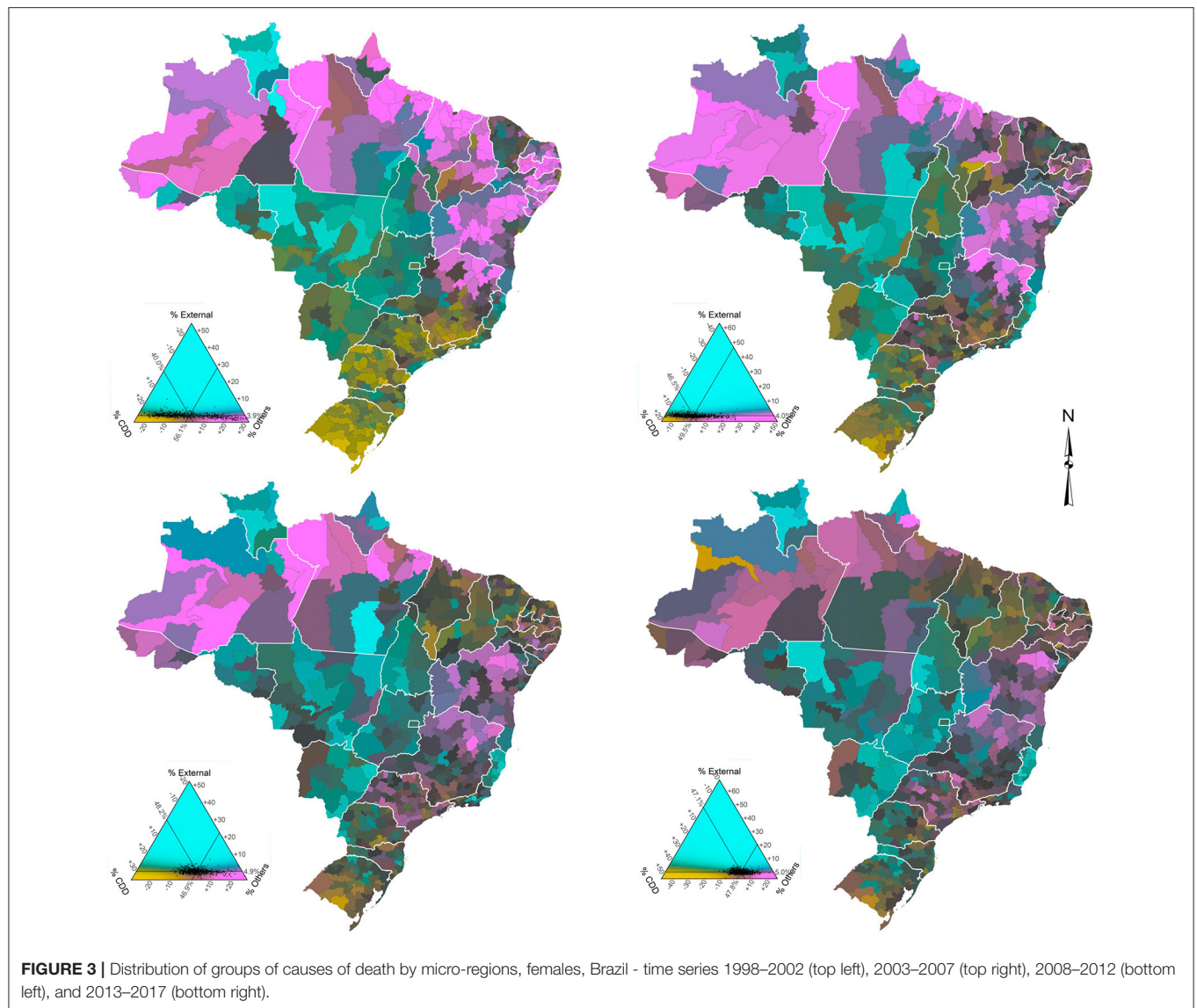
a significant increase in chronic degenerative diseases between 1998–2002 and 2003–2007. In addition, the states of Rio de Janeiro and São Paulo (Southeast) and Rio Grande do Sul (South) were the only ones in these regions that observed a drop in the proportion of deaths from CDDs and an increase in the proportion of deaths from other causes throughout the period. We can also observe that, over the years, the mortality structure of women in micro-regions has converged to the average Brazilian mortality structure, a slightly different situation from what we see for men. In summary, the mortality structure observed in the states that are closest to the average Brazilian mortality structure for women are Ceará (Northeast) - 1998–2002; Piauí, Ceará, Rio Grande do Norte, and Sergipe (Northeast) - 2003–2007; Sergipe (Northeast) and Rio de Janeiro (Southeast) - 2008–2012; and Rondônia (North), Rio Grande do Norte, Paraíba and Alagoas (Northeast) and Rio de Janeiro (Southeast) -2013–2017.

DISCUSSION

In recent years, few studies have investigated the variation of mortality by causes of death in Brazil taking both time and spatial factors into consideration, which makes us understand that further studies in this area are needed. Borges (5) examines health and mortality transitions across regions in Brazil and shows that there is a regional variation in the improvement of mortality from chronic degenerative diseases: faster declines were observed in the Southern regions of the country, but the persistence of high levels of mortality due to infectious diseases remained in the northern parts of the country. Borges (5) also showed the negative impact of external causes of death on the variation in life expectancy across the country. França et al. (6), based on estimates of the GBD study, investigate the trends in mortality and causes of death across states from 1990 to 2017. As in previous studies, they show a rapid increase in life expectancy

and, similar to Borges (5), a variation in the causes of death across regions and over time. However, both studies focus on larger areas and miss important variations within states that are also marked by high income and social inequalities that might affect both the intensity and distribution of different causes of death. The results for regions and states do not represent the differences observed within each area. For instance, in the state of Minas Gerais the results indicate different regional patterns of mortality by cause. Therefore, understanding the spatial pattern of mortality by cause and sex, especially in small areas, becomes extremely relevant for public health policies and the well-being population, as these policies must be elaborated and spatially focused to serve a population that is heterogeneous in its composition, and that, consequently, presents specific and varied demands.

In the last two decades, the distribution of analyzed causes of deaths changed in most micro-regions. In parallel with spatio-temporal variations, there is a significant gender gap in Brazil in relation to mortality. This can be seen in a higher life expectancy at birth for women, which is 7.1 years higher than it is for men (2). Regionally, there are important differences in the trends in causes of deaths and mortality patterns for males and females.

Regarding mortality from external causes, we observed that the impact is, on average, four times greater for males. The results showed that the mortality of males due to external causes has spread to several micro-regions in the North and Northeast regions, while for females the pattern is less clear. This pattern is in line with what is observed in other studies, although, most of those studies are focused on a specific group or category of mortality from external causes (5, 19, 31–36). In the states of the South and Southeast regions, mortality from homicides increased between 1980 and 2000, while in Northern and Northeastern states, violent deaths rose more markedly after 2000 (31–34). At the state level, between 2001 and 2011 in all Northeastern states (except Pernambuco), homicide rates increased (31). Meanwhile, data show that in six states in the North and Northeast regions, homicide mortality more than doubled between 2005 and 2015 (33). On the other hand, the same study indicates homicide mortality diminution in all Southeastern states. Traffic accidents (TA) represent the other main component of mortality from external causes (32, 35, 36). According to Morais-Neto et al. (37), between 2000 and 2010, mortality from traffic accidents increased substantially in Brazil. However, there are clear regional differences in the TA mortality trends (37, 38). Mortality from motorcycle accidents, for example, has increased significantly in North, Northeast, and Center-West regions in recent decades (19, 37, 39). Pinheiro et al. (40) found that, between 2005 and 2015, several municipalities in the western portion of Paraná, passing through the Center-West and Northeast regions, presented a high concentration of high motorcycle mortality rates among women. To some extent, this spatial pattern can also be observed in our findings.

In the last decades, communicable disease mortality in Brazil has been steadily decreasing (6, 7). In states such as Amazonas, Rondônia, Pernambuco, Minas Gerais, Goiás, and Distrito Federal, as well as in all states in the southern region, the disability-adjusted life year (DALY) of neglected tropical diseases rates (infectious and parasitic diseases) fell more than 40% between 1990 and 2016 (7). Leite et al. (41) observed that in 2008 infectious and parasitic diseases represented a large share of DALY in North (18.3%) and Northeast (15.7%) regions. The DALY proportion represented by that group of causes of death in the same regions was 32.7 and 30.1% in 1998, respectively (42). The maps presented seem to agree with these estimates, as other causes of death, such as infectious and parasitic diseases, were still relevant in these regions, even in the last period, although to a lesser extent.

Finally, chronic degenerative diseases, more specifically CVDs and neoplasm, represent ∼47% of all deaths that occur in Brazil (43). In line with other studies, the results show a higher proportional increase in deaths from CDDs in the micro-regions of the North and Northeast, and that men have higher mortality than women (6, 44). Baptista and Queiroz (17, 18) show that less developed regions, such as the North and Northeast, have experienced a more rapid increase in mortality from cardiovascular diseases in recent years. Compared to neoplasms, its contribution to overall mortality has increased steadily from 1991 to 2010, for both males and females (14). The change is closely related to changes in population age structure. Overall, neoplasms are the second major cause of death in Brazil. In 1990, the highest level of mortality due to neoplasm was concentrated in the South region of the country, but a spread in mortality from this cause to all regions was observed by 2010. In 2010, almost all regions in the South and Southeast of the country had very high mortality rates from this particular cause, as did some areas of the Northeast (45). There is variation across regions in the level and the timing of mortality change from causes that directly influence the gender gap. A decline in female mortality from CVDs started first and decreased at higher levels in the states of the Southeast and South regions (5, 13). Throughout 1998-2017, in comparison with males, there was a clear reduction in the number of Southern and Southeastern micro-regions with above average CDD mortality for females (15). In recent years, the decline in CVDs has been related to a decline in risk factors associated with the individuals targeted by policies, such as tobacco control and programs to improve preventive care for high blood pressure (6, 13). However, the quality of hospital care plays an important role in the declining trend and there are large regional differences in assistance quality (13).

The diverse color-coded figures across space and time show the different stages of the epidemiological transition across different regions of the country. Epidemiological transition is not happening uniformly across the country and the prevalence of diseases varies substantially. For instance, for males in 2013-2017, we observe higher levels of external causes of death (homicides and accidents) in the interior and coastal areas of the Northeast. For females, external causes of death are concentrated in the Southeast region, more specifically in micro regions in the state of Rio de Janeiro. This implies that the Brazilian health care system needs to elaborate specific policies and interventions for each area, taking into consideration the demographic dimension, as well as the specificities of the health transition. The previous results indicate that a national health policy, or even a state level one, is not

the best alternative to cover the public health demand in the country.

CONCLUSION

In this paper, our contribution was to study the spatio-temporal evolution of the main causes of death across small areas and over time in Brazil. This is helpful in understanding the dynamics of the health transition in Brazil in a recent period of time and it can have a positive impact on public health policies. Results are in line with other studies that focus on states or major regions of the country, but we provide results for small regions over a relatively long period of time. Mortality levels by different diseases are related to population age structure, health conditions, institutional factors, the environment and the socioeconomic situation to which the population is exposed. Brazil is marked by large socioeconomic differences with strong relations to regional diversities (46). These relations offer possibilities for targeted public interventions, but at the same time present challenges that a country of continental dimensions cannot avoid. Brazilian health-system planning requires an understanding of the absolute burden of the main causes of deaths and the effect of changes in population age structure.

Regional trends in early mortality by chronic and degenerative diseases should be carefully analyzed, so as to better define strategies to address the realities in different regions of the country. Results also showed the transition over time regarding external causes of deaths and the role they play in explaining the gap in male and female mortality. In the context of the Covid-19 pandemic, our results also shed some light on which regions might be more vulnerable to the impacts of the pandemic given the recent trends in causes of deaths, since several studies showed

that individuals with certain comorbidities are more susceptible to more severe cases of the disease.

Finally, the analysis highlights the importance of combining spatial and demographic analysis using data visualization approaches. The map color scheme allows us to study and observe changes in mortality from various causes in the same figure instead of looking at each cause in a different figure. In addition, it combines spatial and temporal analysis, which makes it easier to observe important and interesting trends.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

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Improving the Policy Utility of Cause of Death Statistics in Sri Lanka: An Empirical Investigation of Causes of Out-of-Hospital Deaths Using Automated Verbal Autopsy Methods

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Background: Setting public health policies and effectively monitoring the impact of health interventions requires accurate, timely and complete cause of death (CoD) data for populations. In Sri Lanka, almost half of all deaths occur outside hospitals, with questionable diagnostic accuracy, thus limiting their information content for policy.

Objectives: To ascertain whether SmartVA is applicable in improving the specificity of cause of death data for out-of-hospital deaths in Sri Lanka, and hence enhance the value of these routinely collected data for informing public policy debates.

Methods: SmartVA was applied to 2610 VAs collected between January 2017 and March 2019 in 22 health-unit-areas clustered in six districts. Around 350 community-health-workers and 50 supervisory-staffs were trained. The resulting distribution of Cause-Specific-Mortality-Fractions (CSMFs) was compared to data from the Registrar-General's-Department (RGD) for out-of-hospital deaths for the same areas, and to the Global-Burden-of-Disease (GBD) estimates for Sri Lanka.

Results: Using SmartVA, for only 15% of deaths could a specific-cause not be assigned, compared with around 40% of out-of-hospital deaths currently assigned garbage codes with "very high" or "high" severity. Stroke (M: 31.6%, F: 35.4%), Ischaemic Heart Disease (M: 13.5%, F: 13.0%) and Chronic Respiratory Diseases (M: 15.4%, F: 10.8%) were identified as the three leading causes of home deaths, consistent with the ranking of GBD-Study for Sri Lanka for all deaths, but with a notably higher CSMF for stroke.

Conclusions: SmartVA showed greater diagnostic specificity, applicability, acceptability in the Sri Lankan context. Policy formulation in Sri Lanka would benefit substantially with national-wide implementation of VAs.

Keywords: verbal autopsy, SmartVA, causes of death, Sri Lanka, out-of-hospital deaths, home deaths, cause specific mortality fractions

INTRODUCTION

A well-functioning Civil Registration and Vital Statistics (CRVS) system is fundamental to support the sustainable development of a country. Completeness of vital events registration, as well as the diagnostic quality of mortality data, are the two most important factors determining the proper functioning of CRVS systems (1). Worldwide, only one in four countries have well-functioning death registration systems, primarily in Europe, North America and Australasia (1, 2). Given their critical role in supporting health and development strategies in countries, strengthening CRVS systems has become an urgent policy priority, supported by new and significant investments from philanthropy and other development partners (3).

Cause of death (CoD) information is arguably the most essential component of a CRVS system from a health policy perspective (3, 4). However, globally, only about one-third of all deaths are assigned a cause that is sufficiently specific for informing policy (5). Each year, of the roughly 25 million deaths that are reported by vital registration systems in countries, about 7 million are assigned causes which are of limited use for guiding public health policy and planning, collectively known as "garbage codes" (6–8). Global initiatives such as the Bloomberg Philanthropies Data for Health Initiative (BD4H) have been established to strengthen CRVS systems in lower-and-middle-income countries (LMICs), focussing in particular on improving data collection practices and critical data analysis skills (9, 10). In order to more reliably diagnose the causes of community deaths, an automated diagnostic tool known as "SmartVA Automated Verbal Autopsy" has been trialed in several countries, including Sri Lanka (11).

SmartVA is a method for estimating population-level cause of death patterns. From the information obtained by a trained interviewer from the caretaker of the deceased person, computer algorithms can diagnose the most probable cause of death based on pattern recognition in the data. The interview covers the circumstances, signs and symptoms, and health care seeking behavior of the decedent during the terminal stage leading to death.

Automated VA is the only cost-effective alternative for generating reliable information on cause of death patterns in populations where the medical certification of CoD is not feasible (4). The value of this methodology in improving the evidence base available to countries for policy formulation and evaluation has been recognized by global health development agencies, including the World Health Organization (12).

Validation studies have demonstrated that recall accuracy for symptoms has limited effect on the diagnostic performance of VA up until about 12 months after death (13). Capturing data electronically also reduces data collection time, and data errors (14). The Tariff-method, one of the computer-based algorithms available for the analysis of VA data, has been incorporated into the SmartVA platform, and is the most intuitive and easily understood of the various diagnostic methods available (15). Comparative analyses with physician-assisted diagnosis of VA data have demonstrated the reliability and practicality of automated VA methods for the generation of population level

CoD statistics cheaply, rapidly and in a standardized fashion (4). The Tariff diagnostic algorithm yields diagnoses for 33 mutually exclusive and exhaustive common causes of adult deaths, typically covering about 80-90% of the most common causes of death in LMICs (16, 17).

In some cases, the "signal-to-noise" ratio from the VA interview is too poor to confidently diagnose the most probable cause of death. In these cases, typically 10–15% of all VAs, the cause of death is "undetermined". These deaths can then be reallocated to one of the 33 defined causes based on knowledge about the epidemiology of the population and the comparative ability of the algorithm to identify specific causes (18). Following the re-distribution of undetermined causes, all deaths are assigned a cause and aggregated to yield population -level cause-specific mortality fractions (CSMFs). More detail on the development of the Tariff diagnostic algorithm, on the shortened VA questionnaire, and the development and performance of the SmartVA package, can be found elsewhere (15, 18–20).

As part of the D4H Initiative, the Government of Sri Lanka expressed interest in the potential application of automated VA methods for routinely diagnosing out-of-hospital deaths as a cost-effective alternative to the current practice of assigning a cause of death by non-health officers, often leading to poorly defined causes of death of limited usefulness for policy and planning in the health sector. In order to establish the validity of the methodology, and whether or not it was an improvement on current practice, we compared CSMFs from the application of SmartVA to those from current methods being applied for the determination of CoD of community deaths, for both the Sinhalese and the Tamil-speaking populations. Our primary aim was to ascertain whether SmartVA is applicable in reducing undetermined cause of death data for out-of-hospital deaths in Sri Lanka, and hence enhance the value of these routinely collected data for informing public policy debates.

METHODS

Study Population

Approximately one-half of the 130,000 deaths which occur each year in Sri Lanka take place outside a healthcare facility (21). Under the current CRVS system in Sri Lanka, an appointed divisional-level officer without medical training i.e., the Birth and Death Registrar, assigns a cause to these out-of-hospital deaths based on a brief questionnaire asked of the family of the deceased (22, 23) (**Supplementary Figure 1**). In essence, this system is designed more to ensure that all deaths are registered and given a cause of death than to ensure that an accurate cause has been assigned.

Improving the usability of the CoD data for these out-of-hospital deaths has long been a priority for policy makers and health planners in Sri Lanka. To oversee the trial of SmartVA in Sri Lanka under the D4H Initiative, a Technical Working Group (TWG) on VA was established comprising key local stakeholders (22) who guided the implementation of the study. The main task of the TWG on VA was to advise on study design, including the selection of administrative areas and districts for collecting the

interviews for the different phases of the study, as described in **Supplementary Figure 2**.

The main phase of data collection was preceded by a pilot phase applied to a convenience sample of approximately 300 adult deaths. The main purpose of the pilot was to assess the feasibility of the tablet-based verbal autopsy methodology. The interviews were carried out using Public Health Midwives (PHM), most of whom had not previously been exposed to tablet technology. They did this within the context of their existing domiciliary care-based model using the two local languages. Minor linguistic fine-tuning of the questionnaire was done following this phase.

Subsequently the main-phase of data collection was conducted in 6 districts clustered in the Western/North Western, Central and the Northern parts of Sri Lanka (**Supplementary Figure 3**). One of the districts (Colombo) is further divided into two health administration areas; a Regional Directorate area (i.e., Colombo-RDHS) and a Municipal Council area (i.e., Colombo-CMC). All six divisions of the Colombo-CMC region and two to three areas from other regions were selected for the study based on their representativeness within the district as well as the feasibility of obtaining sufficient cases (**Supplementary Table 1**).

Based on the finding of a relatively high CSMF for stroke among the Sinhalese speaking population sample, modifications were made to the terminology used for some questions relating to possible stroke symptoms, which had arisen when translating the questionnaire. Subsequently, an extended phase was conducted in a sample of deaths in Colombo-CMC area based on this modification.

Instrument and Data Collection

The SMART-VA verbal autopsy questionnaire was used to collect data (19), using the validated and item-reduced shortened version of the Population Health Metrics Research Consortium (PHMRC) data instrument (16, 24, 25). The questionnaire (Sinhalese, Tamil or English) was incorporated into a Smart-tablet using an Open Data Kit application. The questionnaire included 4 main modules;

- Module 1- General module: containing details of the deceased, respondent, characteristics of the death and the interviewer.
- Module 2- Adult module.
- Module 3- Child module.
- Module 4- Neonatal module.

Case definitions were used to divide the deceased into three strata (see **Supplementary Table 2**).

After completing Module 1, the relevant module for each death was automatically selected by the software application based on the age of the deceased. The completed questionnaires were saved in the tablets and transmitted to a central database following verification by a trained supervisor.

The TWG on VA, in consultation with the Director General of Health Services, concluded that the most suitable interviewers for data collection would be the PHM, who are attached to the field health institutions of the Ministry of Health and Indigenous Services (MOH). The PHM are a well-recognized field-staff category in Sri Lanka involved in the delivery of community health services mainly related to the provision of maternal and child health (26). A series of well-structured training programmes was conducted in all selected districts. Each workshop was attended by an average of 20 PHM. Training sessions included practical sessions as well as mock interviews. In addition, ethical considerations and the development of "soft-skills" (i.e., listening skills, empathizing, non-verbal communication etc.) were also included in the curriculum as well as training in using the tablets. A field-based practical session which included each PHM conducting the Smart-VA interview under supervision, was incorporated into all workshops. The Medical Officer of Health, a Public Health Nursing Sister or a Supervisory PHM were also given a 1-day training intended for data collection supervisors.

Ensuring Sustainability

The collection of the VAs was conducted by the MOH and its staff and overseen by the TWG on VA who guided decision making on all logistical as well as administrative aspects, collaborating with University of Melbourne staff for technical inputs. The Registrar General's Department and the Health Information Society of Sri Lanka (HISSL) also assisted with implementation, by providing information about the households that had registered deaths.

The supervisory officers from the MOH were instructed in the resolution of potential issues related to tablets and transfer of data; more complex information-technology (IT) problems arising from the data collection were resolved by health-information experts at HISSL. Operational instructions were negotiated with the district level supervisory officers regarding the involvement of the PHM in data collection without interrupting their routine duties. Approximately 350 PHM were trained and provided with a Smart-Tablet device. In addition, around 50 supervisory officers were trained to oversee data collection and provide quality control checks on the work of the interviewers. The collection of the data proceeded as a service-requirement of the Ministry of Health. Two evaluation workshops were held with data collectors to discuss any challenges experienced in implementing the questionnaire.

Data Analysis

The data were processed by the MOH through the "SmartVA-Analyze" software after duplicate cases were identified and removed, and data were cleaned. Since the number of neonatal and child deaths were insufficient for meaningful interpretation, our analysis is limited to adult deaths (which in any case comprise the vast majority of deaths in the country).

In order to assess the plausibility of the CSMFs derived from application of the SmartVA methodology, the results were compared with estimates from the Global Burden of Disease (GBD) Study for Sri Lanka (27). While this is not strictly a comparable population, since the GBD also includes deaths in hospitals in Sri Lanka, it is the only available data on corrected (for ill-defined causes) CSMFs for Sri Lanka. Since the full list of diagnoses in the GBD cause of death classification differs from that of SmartVA, comparisons of leading causes of death with the GBD were done by mapping the GBD cause to the list of VA causes. The other comparator data set used was home

TABLE 1 | Age distribution of deaths for the VA sample and for out-of-hospital deaths in corresponding areas recorded in the RG data (2014) and estimated by the GBD (2017).

Age group	Total N (%)		
	SmartVA	RG	GBD
12–14*	2 (0.1)	5 (0.1)	357 (0.3)
15–19	8 (0.3)	23 (0.5)	905 (0.7)
20–24	2 (0.1)	35 (0.7)	1,452 (1.2)
25–29	50 (1.9)	38 (0.8)	1,444 (1.2)
30–34	3 (0.1)	46 (0.9)	1,647 (1.3)
35–39	18 (0.7)	39 (0.8)	2,211 (1.8)
40–44	25 (1.0)	76 (1.6)	2,944 (2.4)
45–49	29 (1.1)	105 (2.1)	4,304 (3.5)
50–54	67 (2.6)	211 (4.3)	6,176 (5.0)
55–59	130 (5.0)	231 (4.7)	8,445 (6.9)
60–64	179 (6.9)	389 (7.9)	1,1215 (9.1)
65–69	288 (11.0)	521 (10.6)	14,400 (11.7)
70–74	330 (12.6)	690 (14.1)	15,852 (12.9)
75–79	427 (16.4)	724 (14.8)	15,333 (12.4)
80–84	413 (15.8)	734 (15.0)	15,582 (12.6)
85+	625 (23.9)	1,030 (21.0)	20,947 (17.0)
Unknown	14 (0.5)	1 (0.0)	0 (0)
Total**	2,610 (100.0)	4,898 (100.0)	123,213(100.0)

*For RG and GBD data, this age category was 10–14 years.
**For 2 deaths, sex category is missing in VA.

deaths from the sampled districts identified in the latest available (2014) annual data set from the RG Department. These data were entered into the ANACONDA software (28) to identify the leading causes of home deaths.

RESULTS

It was demonstrated that despite having little or no experience with tablets, it was possible to train 350 data collectors to competently carry out interviews with tablets and having these uploaded to a central server in the Ministry without any significant IT problems being reported. In the two evaluation workshops, no refusals were reported and the additional time burden for the PHMs was judged acceptable.

A total of 2,623 VAs were performed for adult deaths, and of these, 2,610 cases (1,250 male, 1,358 female, 2 sex unknown) met the analytical pre-requisites for SmartVA-Analyze. The median (IQR) age at death in the adult sample was 74 (64 to 82) and 79 (70 to 86) years for males and females, respectively. No respondents refused the VA interview.

The age-at-death distribution is given in **Table 1**. For comparison, the age-distribution of out-of-hospital deaths for corresponding areas from the Registrar General-(RG) data for 2014 is also shown, along with the estimated age-distribution of deaths for Sri Lanka in the GBD Study.

Of the 2,610 adult VAs, a cause of death could not be determined for 362 (13.9%), more so for females (16.9%) than

TABLE 2 | Cause specific mortality fractions (after-redistribution of undetermined cases), adult deaths, Sri Lanka, 2017–18.

Cause	Total (%)	Male (%)	Female (%)
Stroke	33.9	31.6	35.4
Ischemic heart disease	13.5	13.5	13.0
Chronic respiratory	13.1	15.4	10.8
Diabetes	8.2	6.7	9.5
Other non-communicable diseases	3.3	3.1	3.4
Chronic kidney disease	3.1	4.2	2.0
Falls	3.0	1.9	3.9
Lung cancer	2.4	4.0	0.9
Diarrhea/dysentery	2.2	1.7	2.5
Pneumonia	2.2	2.1	2.2
Esophageal cancer	1.9	2.6	1.2
Other injuries	1.5	1.3	1.5
Prostate cancer	1.5	3.0	0.0
Cervical cancer	1.4	0.0	2.6
Leukemia/lymphomas	1.1	1.2	0.9
Breast cancer	1.0	0.0	2.0
Stomach cancer	1.0	0.9	1.1
Cirrhosis	0.9	1.4	0.5
Other cancers	0.9	0.9	1.0
TB	0.8	1.1	0.6
Other infectious diseases	0.7	0.5	0.8
Other cardiovascular diseases	0.5	0.3	0.6
Poisonings	0.4	0.3	0.5
Colorectal cancer	0.3	0.3	0.4
Homicide	0.3	0.2	0.3
Road traffic	0.3	0.3	0.2
Suicide	0.3	0.3	0.2
Drowning	0.2	0.2	0.2
Fires	0.1	0.1	0.2
Bite of venomous animal	0.0	0.0	0.0
Maternal	0.0	0.0	0.1

for males (10.5%). **Table 2** shows the CSMFs for adult deaths in the sample after re-distributing the undetermined causes according to the algorithm proposed by Serina et al. (18). Stroke, chronic respiratory diseases, ischemic heart disease, and diabetes were identified as the leading causes of death in this sample of home deaths, followed by other non-communicable diseases, collectively accounting for almost three-quarters (72%) of all adult deaths.

To assess the plausibility of the age-patterns of causes of death in the sample, **Supplementary Figures 4A,B** compares the age-distribution of the three leading causes of death diagnosed by SmartVA with what the GBD reports for the same causes.

We also assessed the plausibility of the CSMFs from SmartVA by comparing the leading causes of death, by sex, with what has been estimated for Sri Lanka by the GBD (**Figures 1A,B**). While for many causes of death, the cause fractions are reasonably similar, they are substantially different for the three leading causes, Stroke, IHD and Chronic respiratory disease, more so for
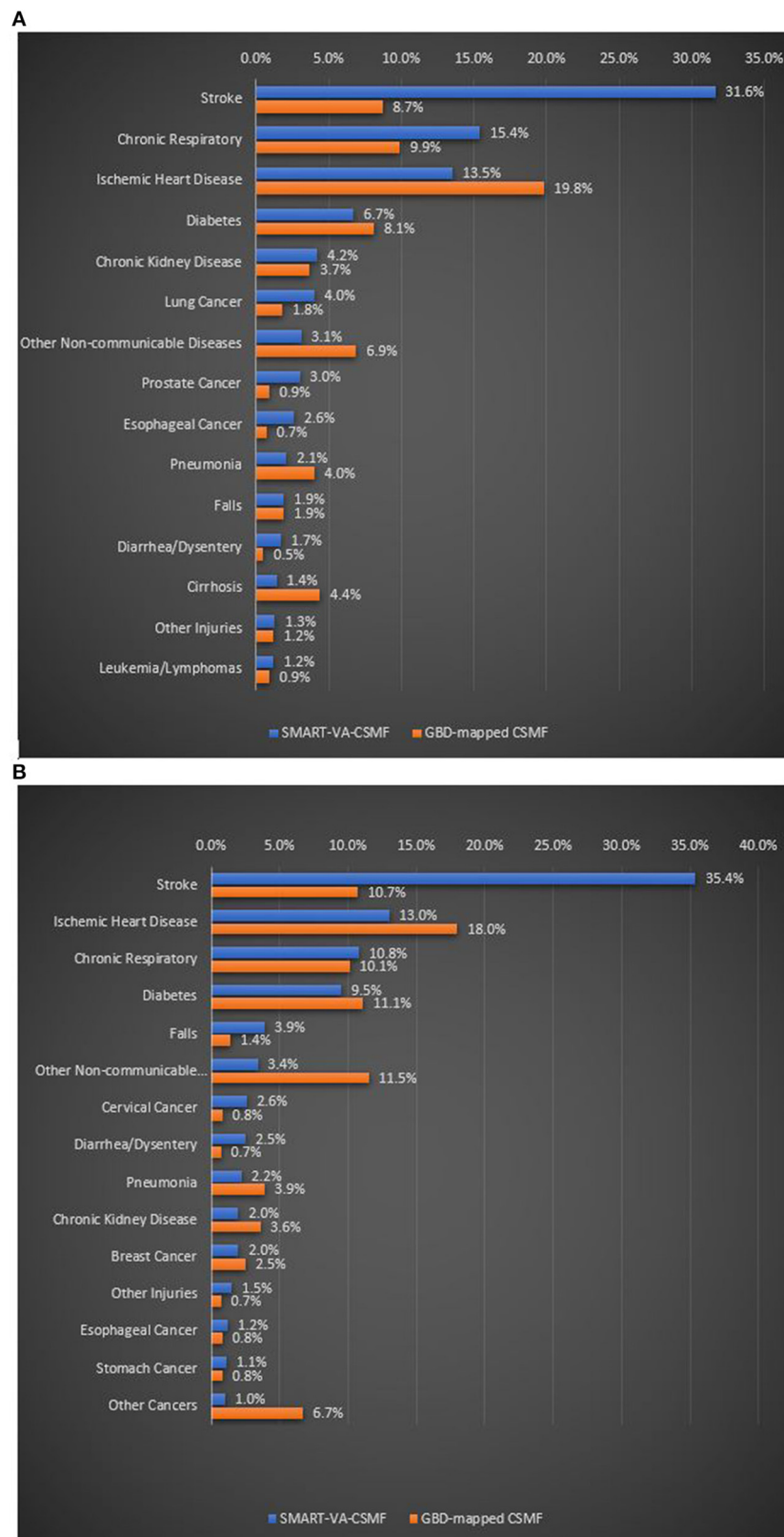
FIGURE 1 | (A) Leading 15 CSMFs for adult males estimated by SmartVA and the GBD, Sri Lanka, 2017–18. **(B)** Leading 15 CSMFs for adult females diagnosed by SmartVA and the GBD, Sri Lanka, 2017–18.

Areas with Sinhalese as the main language		Areas with Tamil as the main language	
Cause	%	Cause	%
Stroke	37.0	Stroke	22.0
Chronic respiratory	12.4	Ischemic heart disease	19.5
Ischemic heart disease	12.4	Chronic respiratory	11.5
Diabetes	8.2	Diabetes	8.8
Other non-communicable diseases	3.3	Chronic kidney disease	6.6
Falls	3.0	Pneumonia	4.9
Chronic kidney disease	2.7	Other non-communicable diseases	3.5
Diarrhea/dysentery	2.4	Lung cancer	3.5
Lung cancer	2.2	Esophageal cancer	2.9
Esophageal cancer	1.8	Prostate cancer	2.0

males. For stroke in particular, SmartVA estimates a much higher fraction of deaths than the GBD. While some of this difference undoubtedly arises due to the older age structure of out of hospital deaths in the VA sample, the differences are sufficiently large to suggest systematic under-estimation of stroke deaths by the GBD and possibly a tendency to over-diagnose stroke deaths by SmartVA. For females, stroke was also substantially higher in the VA sample than in the GBD, while the converse was true for IHD. For females, CSMFs for chronic respiratory disease (and diabetes) were similar.

The stroke: IHD mortality ratio was reversed between the two sets of estimates, being substantially >1 for the VA population, as diagnosed by SmartVA, and <1 according to the GBD. In part, this could be due to the very old age structure of the VA sample deaths. **Table 3** compares the CSMFs of the 10 leading causes according to the main-language related geographical areas. CSMFs for ischemic heart disease, chronic kidney disease and pneumonia were notably higher for the (Tamil) areas of the Northern cluster compared to areas where Sinhalese was used as the main language. The fraction of deaths due to stroke was higher among the Sinhalese-speaking population. Interestingly, the stroke: IHD mortality ratio was much closer to one for the Tamil speaking areas than for the Sinhalese speaking populations.

In order to investigate whether the wording change made when translating the questionnaire had had a significant impact on the CSMF for stroke, we compared, for the Colombo CMC population only, the CSMFs of VAs from the main phase with those collected following the slightly amended questionnaire in the extended phase, as shown in **Figure 2**. While stroke still remained the leading cause of death in the extended phase, the CSMF decreased substantially from 37.5 to 28.6%, between the two samples. The converse was true for chronic respiratory diseases. Although based on a relatively small sample size (250 deaths), this analysis suggests that the CSMF for stroke may have been overestimated by as much as 25–30% due to the rewording of the Sinhalese questionnaire following the pilot phase. This

should be kept in mind when interpreting the results of the main study and may partially explain the difference in the CSMFs compared with the GBD.

In order to assess the policy utility of SmartVA, we calculated the amount of "garbage codes," (i.e., codes with no or limited value for public health policy and planning) in the RG data for 2014, taken from the same geographical areas as the SmartVA sample (**Table 4**). Based on current practice for deaths which are not medically certified, nearly 65% of male deaths and 75% of female deaths were assigned a cause of death that has little or no policy value. In Sri Lanka, the leading "garbage codes" which severely limit the policy value of the data include senility, cardiac arrest & shock, hemi/para/quadriplegia, and heart failure. In stark contrast, only about 10% of male adult deaths, and 17% (one in six) of female deaths, many of them at very old ages, could not be diagnosed with a specific cause using SmartVA. In other words, SmartVA reduced the fraction of home death diagnoses that are of no or little value for guiding policy by about 85% for males, and 75% for females.

DISCUSSION

Although the SmartVA methodology has been applied in several countries (11) to diagnose the leading causes of community deaths, it was particularly important to demonstrate its feasibility in Sri Lanka to improve the specificity of causes of death data for home deaths, given the relatively large fraction (nearly 50%) of all deaths that they comprise (21). Our study, conducted in diverse settings and in the two main language groups of Sri Lanka, demonstrated the feasibility and value of the methodology in identifying the most probable causes of out-of-hospital deaths in the country, suggesting a vastly different epidemiological pattern to that based on current practice. Around 40% of deaths diagnosed by the RG staff under current practice were assigned "garbage codes" classified as having "serious or substantial impact" for misguiding policy debates, compared with 14% of cases for which SmartVA could not determine the cause of death.

In order to assess the plausibility of the SmartVA findings on mortality patterns, we compared the direct evidence produced by the method with the estimates from the GBD Study, which makes extensive use of covariates to model disease and injury patterns, as well as adjustments to the data to correct for misdiagnoses (5). Given the similarity of age at death distributions across all three data sources (VA, RG and GBD) there is unlikely to be a major age-structure effect on comparisons of CSMFs between SmartVA and current practice (RG data), although the markedly higher fraction of deaths at the oldest ages in the VA sample could bias upwards CSMFs for causes such as stroke which dominate at these ages. The age patterns of mortality for each of three leading causes of death calculated from SmartVA are very similar to what might be expected based on the extensive epidemiological consistency adjustments that characterize the GBD (5), with a progressive rise in the number of deaths with advancing age. The exceptional decline in the proportion of male deaths from ischaemic heart disease after age 80 is similarly observed in the GBD estimates and would appear to be real.
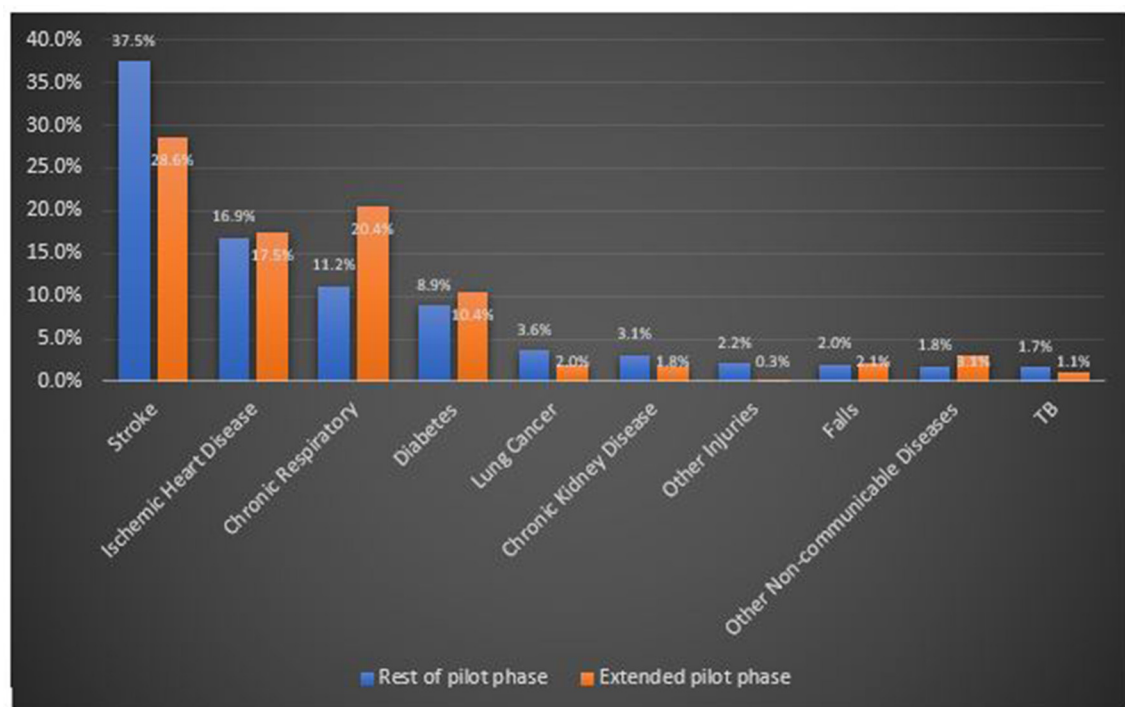
FIGURE 2 | Comparison of the 10 leading causes of death diagnosed by SMARTVA in the Colombo CMC area before and after modification of the terminology used for stroke symptoms.

TABLE 4 | "Garbage codes" classified according to four severity levels among out-of-hospital deaths in the VA areas.

Severity level	Both sexes N (%)	Males N (%)	Females N (%)
Very high[a]	1,681 (34.1)	724 (29.3)	957 (38.9)
High[b]	375 (7.6)	167 (6.8)	208 (8.5)
Medium[c]	784 (15.9)	434 (17.6)	350 (14.2)
Low[d]	629 (12.8)	301 (12.2)	328 (13.3)
Total	3,469 (70.4)	1,626 (65.8)	1,843 (74.9)

Source: Registrar general 2014 data; Total deaths = 4,929; 2,470 males, 2,459 females.
*[a] Very High (Level 1), Garbage codes with **serious impact**: causes for which the true underlying cause of death could in fact belong to more than one broad cause group.*
*[b] High (Level 2), Garbage codes with **substantial impact**: causes for which the true cause of death is likely to belong to only one or two of the three broad groups.*
*[c] Medium (Level 3), Garbage codes with **important impact**: causes for which we know that the true underlying cause of death is likely to be one within the same ICD chapter.*
*[d] Low (Level 4), Garbage codes with **limited impact**: in this case, the uncertainty of diagnosis of the true cause of death is likely to be confined to a single disease or injury category.*

Application of automated verbal autopsy methods to diagnose community deaths in Sri Lanka would likely have many other benefits for improving the information base for policy. Currently, the compilation of national-level data on out-of-hospital deaths through the civil registration system is time consuming, with the result that data are generally well-out of date; for example, as of the end of 2018 when this study was undertaken, the latest available data from the RG's Department referred to 2014. On the other hand, SmartVA being an automated procedure, provides data in real time, and does so cost-effectively (the only additional cost being the purchase of tablets and the costs for training of interviewers), and in a standardized fashion, without the need for physician involvement. In short, our study has demonstrated the feasibility and policy utility of the outputs generated from applying SmartVA routinely for all home deaths in Sri Lanka, providing much greater specificity in causes of death compared with current practice. While we have shown that automated verbal autopsy methods can help increase the policy value of mortality data for community deaths, careful validation studies should be periodically conducted to ascertain the diagnostic accuracy, not only of verbal autopsy information, but also of deaths medically certified in hospitals.

Given the advanced stage of epidemiological transition characterized by relatively low mortality in Sri Lanka, the divergences from the GBD estimates require further investigation. There are several possible reasons for this. First, the GBD estimates refer to all deaths (either at home or in hospital) and the extent to which hospital deaths might have a different cause structure than home deaths would certainly affect this comparison. This might well be the case for stroke deaths and chronic respiratory diseases, which are much more common in elderly populations. Indeed, the VA population included a much higher proportion of deaths above age 80 compared to what was estimated by the GBD, including hospital patients who return home to die. Common causes of death at these advanced ages are likely to be stroke and COPD. Further, the data sources used in the GBD covariate modeling processes

for Sri Lanka might be biased toward IHD as a diagnosis over stroke, leading to artificially low CSMFs for stroke. This would require a detailed investigation of how the GBD cause of death models for Sri Lanka have been developed. Finally, the higher stroke CSMFs from SmartVA are likely to be in part artefactual, resulting from the changes in terminology applied to some of the stroke symptom questions after the pilot study. These changes may well-have led to an inflation of the stroke CSMF by about one-quarter for the Sinhalese speaking population. While this would not affect our primary conclusions about the importance of stroke as the leading cause of home deaths in Sri Lanka, it would imply stroke CSMFs that were somewhat closer to the GBD.

There are several limitations of our study that should be mentioned. Firstly, although all data collectors underwent the same training, differences in aptitude, commitment and comprehension among interviewers may have affected the comparability of the findings across population subgroups. Secondly, despite the rigorous translation procedures applied context-specific linguistics may have affected the clarity of some of the questions from the respondents' perspective, this risk was emphasized in all trainings and the data collectors were empowered to convey the expected meaning of each question in cases of uncertainty by the respondent. Finally, the difference in time period between the reference data set as collected by the BDR (2014) and the deaths diagnosed by SmartVA (2017-18) might have led to some bias in the comparisons of cause –specific fractions between the two data sources. This is unlikely to have been substantial, however, given the fact that the vast majority of deaths in Sri Lanka are attributable to non-communicable diseases, which typically change only slowly, and in the absence of any significant shocks from disease pandemics, or natural disasters, in either dataset.

CONCLUSIONS AND RECOMMENDATIONS

Automated verbal autopsy methods can feasibly be applied in Sri Lanka to generate much more reliable and standardized information on the causes of home deaths, and more rapidly, than current practice. We were able to generate over 2,500 VAs by training 350 data collectors from diverse areas of the country to competently carry out family interviews, typically in <30 min, using tablets, and to upload the data to a central server for analysis. Despite having little or no experience with tablets, the PHMs had no difficulty in operating them and no significant IT problems were reported.

The results obtained from the application of SmartVA in Sri Lanka, particularly the much greater diagnostic specificity of diagnoses for home deaths compared with current practice, the overall plausibility of the findings in the context of Sri Lanka's epidemiological transition, the cultural acceptability and effectiveness of the interviews, collectively support the application of SmartVA throughout Sri Lanka as routine practice to supplement current procedures in order to dramatically improve the utility of CoD data for out-of-hospital deaths. Health information systems in Sri Lanka that support policy formulation and evaluation would benefit substantially from the nationwide implementation of SmartVA, with context-based customizations to facilitate sustainability.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because these data are owned by the Ministry of Health of Sri Lanka and any application for acess to these data would need to be addressed to the Ministry of Health in Sri Lanka. Requests to access the datasets should be directed to Sridharan Sathasivam, drsri94115@gmail.com.

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because not applicable as the investigation was implemented as a service requirement. Data were anonymized and irreversibly de-identified. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LM, SA, SS, VK, RJ, DM, and AL conceived the design of the technical activity. AT, PK, KJ, VK, and RJ oversaw the implementation. LM, VK, RJ, RH, RW, MD, CS, and PM contributed in training of data collectors. VK, RJ, SG, RH, RW, MD, CS, and PM were involved in activities related to coordination of data collection and data cleaning. VK, RJ, MD, and PM were involved in data analysis. SA, SS, VK, AT, PK, KJ, and SG provided feedback on data analysis. LM, AL, DM, and PM contributed in drafting the initial manuscript. All authors contributed to the framework construction, results interpretation, manuscript revision, and approved the final version of the manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.591237/full#supplementary-material

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A Web-Based Tool for Quantification of Potential Gains in Life Expectancy by Preventing Cause-Specific Mortality

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Introduction: Local health departments are currently limited in their ability to use life expectancy (LE) as a benchmark for improving community health. In collaboration with the Baltimore City Health Department, our aim was to develop a web-based tool to estimate the potential lives saved and gains in LE in specific neighborhoods following interventions targeting achievable reductions in preventable deaths.

Methods: The PROLONGER (Im**PRO**ved **LONGE**vity through **R**eductions in Cause-Specific Deaths) tool utilizes a novel Lives Saved Simulation model to estimate neighborhood-level potential change in LE after specified reduction in cause-specific mortality. This analysis uses 2012–2016 deaths in Baltimore City residents; a 20% reduction in heart disease mortality is shown as a case study.

Results: According to PROLONGER, if heart disease deaths could be reduced by 20% in a given neighborhood in Baltimore City, there could be up to a 2.3-year increase in neighborhood LE. The neighborhoods with highest expected LE increase are not the same as those with highest heart disease mortality burden or lowest overall life expectancies.

Discussion: PROLONGER is a practical resource for local health officials in prioritizing scarce resources to improve health outcomes. Focusing programs based on potential LE impact at the neighborhood level could lend new information for targeting of place-based public health interventions.

Keywords: life expectancies, neighborhood, local health, mortality reduction, web-based tool

INTRODUCTION

Local health departments play a fundamental role in delivering public health services and frequently employ neighborhood-based strategies to allocate interventions in order to maximize overall population health using limited resources (1). In US cities, population health profiles vary tremendously by neighborhood, shaped by the intersection of socio-political history, natural and built environment, and population features (2).

Life expectancy (LE) is a core measure of the overall health status of a population. LE at birth is defined as the average number of years a newborn is expected to live, assuming the current mortality rates are unchanged over the newborn's lifespan. Unfortunately, not all regions or subpopulations within the US experience the same LE (3, 4). Using Baltimore City, Maryland as an example, the average LE at birth in 2016 was 73.2 years, 5.7 years lower than the US's average of 78.9 and 5.9 years lower than Maryland's average of 79.1 years (4–6). Within Baltimore City's Community Statistical Areas (CSAs), geographic groupings of neighborhoods in the city, the 2016 LE ranged from 66.4 years in Downtown/Seton Hill, an inner-city neighborhood in West Baltimore, to 85.2 years in Cross-Country/Cheswolde, a neighborhood on the city's northern border approaching the wealthy suburban communities in Baltimore County. This represents a nearly 20-year LE gap between two neighborhoods in the same city, located just 6 miles apart (4).

Averting preventable deaths with interventions targeting modifiable or preventable risk factors is an actionable goal for local public health officials. Many local health departments are able to identify leading causes of preventable mortality at a neighborhood level. For example, in the 2017 Baltimore City Neighborhood Health Profiles, the Baltimore City Health Department (BCHD) highlighted CSA-level differences in rates of leading causes of death (7). The CSA of Downtown/Seton Hill had among the highest rates of breast cancer and stroke deaths, while the CSA of Cross-County/Cheswolde had high rates of mortality from prostate cancer and HIV. Comparing leading causes of mortality by neighborhood shifts the focus for community members and local health officials to think about how to target efforts to improve health in each community, rather than focusing exclusively on those communities with the poorest overall health indicators (8).

Local health departments are currently limited in their ability to use LE as a benchmark for improving community health. With a straightforward way to forecast LE gains to be expected from intervening on a cause of death, health departments could target evidence-based interventions to maximize potential lives saved and LE gained within neighborhoods. In collaboration with the BCHD, we developed a web-based tool named PROLONGER (Im**PRO**ved **LONGE**vity through **R**eductions in Cause-Specific Deaths) to estimate the potential lives saved and gains in life expectancy in specific neighborhoods following interventions targeting achievable reductions in preventable deaths. In this paper, we explain the methodology used in the development of this tool and illustrate its use with Baltimore City's cause-specific mortality data as a case-study.

METHODS

In this section, we describe the calculations and model specifications used in the web-based tool, as well as details about the setting (Baltimore City, Maryland) in which we demonstrate this tool. All calculations were done using R Version 3.5.2, and the tool was developed using the RShiny package. This project was reviewed by the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health and determined not to constitute Human Subjects Research.

Mortality, Population, and Observed Life Expectancy

To use the PROLONGER tool, an end-user must upload mortality data, either at the individual-level or aggregated by geographic unit. These data are usually obtained from a city or state vital statistics department. Users choosing to upload individual-level (de-identified) data would need to include the following variables: year of death, age at death, ICD-10 cause of death, and geographic unit of residence at time of death. Users seeking information disaggregated by sex and/or race would need to include those categories as well. Understanding that many end-users may not have access, permission, or feel comfortable uploading individual-level mortality data, we demonstrate aggregated (by year and 5-year age categories until age 85+) mortality data is a feasible alternative.

Population estimates by age category are necessary for calculating mortality rates and life expectancy estimates. CSAs in Baltimore City are aligned with US Census Tracts. Therefore, the tool uses annual population estimates developed by the US Census Bureau from the annual American Community Surveys, which are available disaggregated by sex, race and age category at the Census Tract level (9). If a user is interested in obtaining LE estimates for neighborhoods in which boundaries do not align with those of the US Census Bureau, the user would need to upload population numbers by age category as well.

Observed at-birth LE is estimated by the tool using the Chiang methodology, shown to be optimal for the calculations of LE in small populations of 5,000 or less (10, 11).

Proportion of Deaths Averted

For each cause of death, the tool provides lives saved and LE estimates resulting from averting 5, 10, 15, and 20% of a single cause of preventable deaths. These values were chosen as potentially achievable goals of mortality reductions using evidence-based screening and prevention strategies. The end-user can compare the potential impact of an intervention, as quantified by potential lives saved and LE gained, given different potential levels of mortality burden reduction from a chosen program.

When imposing a reduction in deaths, the optimal way to preserve the exact age distribution of disease-specific mortality would be to reduce deaths in each age category by the chosen percentage. However, this is not realistic from a programmatic perspective. For example, most cardiovascular disease prevention programs are not designed for implementation across all age groups equally, but rather are likely to target middle-aged individuals. Therefore, we compared imposing a reduction in deaths overall vs. within each age category using the R^2 coefficient.

Calculation of Lives Saved

In the tool, the **LI**ves **S**aved **S**imulati**O**n (LISSO) model is used to estimate the potential number of lives saved if success is achieved in reducing preventable deaths. Details of the development of

the LISSO model have been published elsewhere (12). Briefly, we adapted the model employed by Case and Deaton to show potential changes in survival given aversion of cause-specific deaths while still allowing those survivors to age into older age categories and face the same subsequent mortality risk as their peers (13). Expected mortality rates after averting a proportion of cause-specific deaths were calculated by multiplying observed mortality rates by the proportion of lives saved for the index year. The individual lives saved were followed into subsequent years with removal of the proportion of those lives saved that would experience death from the same mortality rate as their peers in those years. Unique to the LISSO model is the inclusion of an agent-based 100-fold simulation step in which the specific individuals that survive are randomly selected. The median number of lives saved from the 100 simulations is used in the subsequent LE calculations.

Calculation of Expected Life Expectancy

The tool then calculates expected at-birth LE following aversion of specified proportions of deaths (5, 10, 15 or 20%) using the same Chiang methodology (11).

The challenge of calculating LE at a neighborhood level is cells that have either 0 or a very small number of deaths attributable to a specific cause, which can artificially inflate the resulting LE. Therefore, all cells with <5 deaths were replaced with a predicted number of deaths calculated using a negative binomial regression model including the following CSA-level covariates for Baltimore City (derived from the US Census Bureau) (9): age at start of the age interval, total age-specific population, proportion of non-Hispanic Black/African American race, proportion of non-Hispanic white race, median household income, and proportion of educational attainment above high school. Less than 5 deaths per cell was chosen as the appropriate cut-off for replacement in line with the CDC's life expectancy calculation methods, in which smoothing techniques are applied to estimate similarly low observed numbers of deaths (14). In cases where the predicted number was greater than the total number of deaths due to the selected cause in that age category, the number was replaced with the total number of deaths.

Individual vs. Aggregate-Level Death Data

We anticipate that, given laws protecting personal health information, local health departments or agencies may not want to upload de-identified individual-level vital statistics data to a web-based tool. The LISSO model was developed for individual-level data, as the model simulates a random selection of specific individuals to "survive" for each estimate of lives saved. In order to accommodate both individual-level as well as aggregate-level death data, we made the following modification in the PROLONGER tool.

With aggregate level data, we made the conservative assumption that the deaths in that age category occurred in a uniform distribution across the 5-year age range. For race and/or sex disaggregated LE calculations, the race and sex distributions are allocated to age groups in the same stratum-specific proportions as the deaths in that age group; within each age group, the deaths are once again distributed uniformly. To test the assumption that aggregate and individual-level data result in similar LE calculations, we calculated R-squared coefficients relating predicted deaths and LE produced from the aggregate models to estimates from the individual-level models.

Tool Interface

The tool interface provides users with tabbed selections of whether they would like to estimate potential LE gains for various causes of mortality in a specific geographic location, or if they would like to select a specific cause of mortality to target and have the tool select the locations that would have the greatest LE benefit. Within each tab, the user selects whether they have individual-level or aggregate-level data, and then is able to choose the percent of cause-specific deaths they believe their intervention would prevent. In addition, the user is able to select whether they would like to see the LEs stratified by sex and/or race.

The tool provides results in tabular form, as well as bar graphs and maps, available for export by the end-user. Finally, there is a tab within the tool detailing the methodology and code used to create the tool.

Case Study: Geographic Area

Because the boundaries of a "neighborhood" can differ by personal opinion, the Baltimore Data Collaborative and the Baltimore City Department of Planning systematically developed boundaries for 55 Community Statistical Areas (CSAs) with Baltimore City, Maryland for which sub-city level data could be calculated. Each CSA contains 1–8 demographically homogenous Census Tracts, with total populations of 5,000–20,000 residents. The CSA boundaries were initially developed in 2000, and last modified in 2010. These are the neighborhood units used by BCHD for sub-city level publications such as the Neighborhood Health Profiles, as well as by several other organizations publishing sub-city level information (4, 7).

Case Study: Deaths

Information from all death certificates filed for Baltimore City residents is compiled by the Maryland Vital Statistics Administration. Vital statistics data for Baltimore City are released annually to the Baltimore City Health Department. Study co-investigators based at the Baltimore City Health Department ran the tool's code using individual- and aggregate-level vital statistics data on site. All Baltimore City deaths that occurred between 2012 and 2016 that are assigned a census tract of residence and have an ICD-10 code for cause of death were included in this analysis. The Maryland Vital Statistics Administration (VSA) codes all reported deaths by cause using the 10th revision of the International Classification of Disease (ICD-10) system (6).

Case Study: Leading Preventable Causes of Death

In the Baltimore City 2017 Neighborhood Health Profiles, the leading underlying causes of death included heart disease (24.4% of all Baltimore City deaths), cancer (all kinds, 21.3%), lung cancer (5.9%), stroke (4.9%), drug- and/or alcohol-Induced

(4.5%), chronic lower respiratory disease (3.5%), accident (3.5%), homicide (3.5%), diabetes (3.0%), septicemia (2.7%), colorectal cancer (2.0%), HIV/AIDS (1.8%), breast cancer (1.5%), prostate cancer (1.1%) (7).

RESULTS

Model Specifications

Overall vs. Within-Age-Group Reduction in Deaths

When imposing a reduction in deaths, the optimal way to preserve the exact age distribution of disease-specific mortality would be to reduce deaths within each age category by the chosen percentage. However, this is not realistic from a programmatic perspective. For example, most cardiovascular disease prevention programs are not designed for implementation across all age groups equally, but rather are likely to target middle-aged individuals. Therefore, we quantified the difference between imposing a 20% reduction in heart disease deaths, comparing a reduction to the overall number vs. applying the 20% reduction within each age group. Both the total deaths as well as the calculated expected LE were extremely similar using both methods ($R^2 = 1$).

Aggregate vs. Individual-Level Data

We tested whether the model would yield similar results if a health department were to upload aggregate death tables as opposed to individual-level data. In order to recreate the simulation for which lives were saved when aggregate death tables were used, the tool creates a pseudo-dataset under the conservative assumption that all deaths within an age group are evenly distributed across that 5-year age group. Using a 20% reduction in heart disease deaths as the test, the calculated expected LEs were compared with aggregate and individual data. The R^2 between expected number of deaths using individual-level vs. aggregate-level data was 0.999. When comparing expected LEs, the R^2 was 0.998. Thus, there was a high degree of correlation in both expected number of deaths and expected LEs whether calculated using aggregate or individual-level data.

CASE STUDY: BALTIMORE CITY FINDINGS

For this case study, we examined applying the PROLONGER tool to Baltimore City, Maryland, using a 20% reduction in heart disease mortality. Interestingly, the neighborhoods where we see the greatest potential LE increases from reductions in heart disease mortality were not the same neighborhoods identified purely by burden, demonstrating the power of the PROLONGER tool to inform the allocation of resources to maximize population health gains.

As with most other areas in the United States, heart disease is the leading cause of death in Baltimore City. **Table 1** shows the ten CSAs with the highest crude heart disease mortality rates annualized over the 2012–2016 time period. The highest heart disease mortality rates of 4.3 per 1,000 occurred in Morrel Park/Violetville and Pimlico/Artlington/Hilltop (**Figure 1A**).

Figure 1B shows the 10 CSAs with the largest expected increase in LE following a 20% reduction in heart disease

TABLE 1 | Ten Baltimore city community statistical areas (CSAs) with the highest crude heart disease mortality rates (per 1,000 population)–2012–2016.

CSA	Crude heart disease mortality rate (per 1,000 population)
Morrell Park/Violetville	4.3
Pimlico/Arlington/Hilltop	4.3
Clifton-Berea	4.0
Greenmount East	3.8
Greater Rosemont	3.7
Greater Mondawmin	3.6
Oldtown/Middle East	3.5
Edmondson Village	3.4
Howard Park/West Arlington	3.4
Dorchester/Ashburton	3.3

in each CSA along with their observed LE. Highlandtown, Orangeville/East Highlandtown, Inner Harbor/Federal Hill, and Greater Charles Village/Barclay emerged as the best targets for overall interventions aimed to reduce heart disease based on the greatest potential increase in LE. This is in stark contrast to the CSAs that would be targeted for intervention based on heart disease mortality rates alone (**Figure 1A**). Morrel Park/Violetville and Pimlico/Artlington/Hilltop, which have the highest heart disease mortality rates, are not even in the top 10 of the expected change in LE following implementation of this hypothetical intervention. Following a 20% reduction in heart disease in each CSA, the median change in LE was 1.35 (IQR: 1.15, 1.58) years.

Notably, it was not always the CSA with the lowest observed LE that would expect the greatest change in LE with a hypothesized 20% reduction in heart disease mortality. **Figure 2** shows that a nearly 2.5-year increase in LE could be expected in Highlandtown even though Highlandown's observed LE is higher than that of Madison/East End, where a smaller 2.0-year increase could be expected. It is true that the CSAs in which higher proportions of deaths due to a cause of interest occur in younger populations would expect greater LE benefits by preventing deaths from that cause. However, we note that those CSAs with an overall younger age distribution did not always emerge as the neighborhoods with the largest expected increases in LE from a 20% reduction in heart disease deaths. In fact, nearly half (49%) of Baltimore City's 55 CSAs had younger population distributions (i.e., lower proportions of the total population aged 65+ years) than Highlandtown and Inner Harbor/Federal Hill.

Similar results were noted when disaggregating the population by sex or race (data not shown).

DISCUSSION

Working collaboratively with the Baltimore City Health Department, we developed a web-based PROLONGER tool that calculates neighborhood-level LE given mortality and population data that is uploaded by the end-user. While there are other tools that will calculate small-area life expectancy

FIGURE 1 | Ten Baltimore city community statistical areas (CSAs) with highest crude heart disease mortality **(A)** and ten CSAs with greatest potential increase in life expectancy following a 20% reduction in heart disease deaths **(B)**.
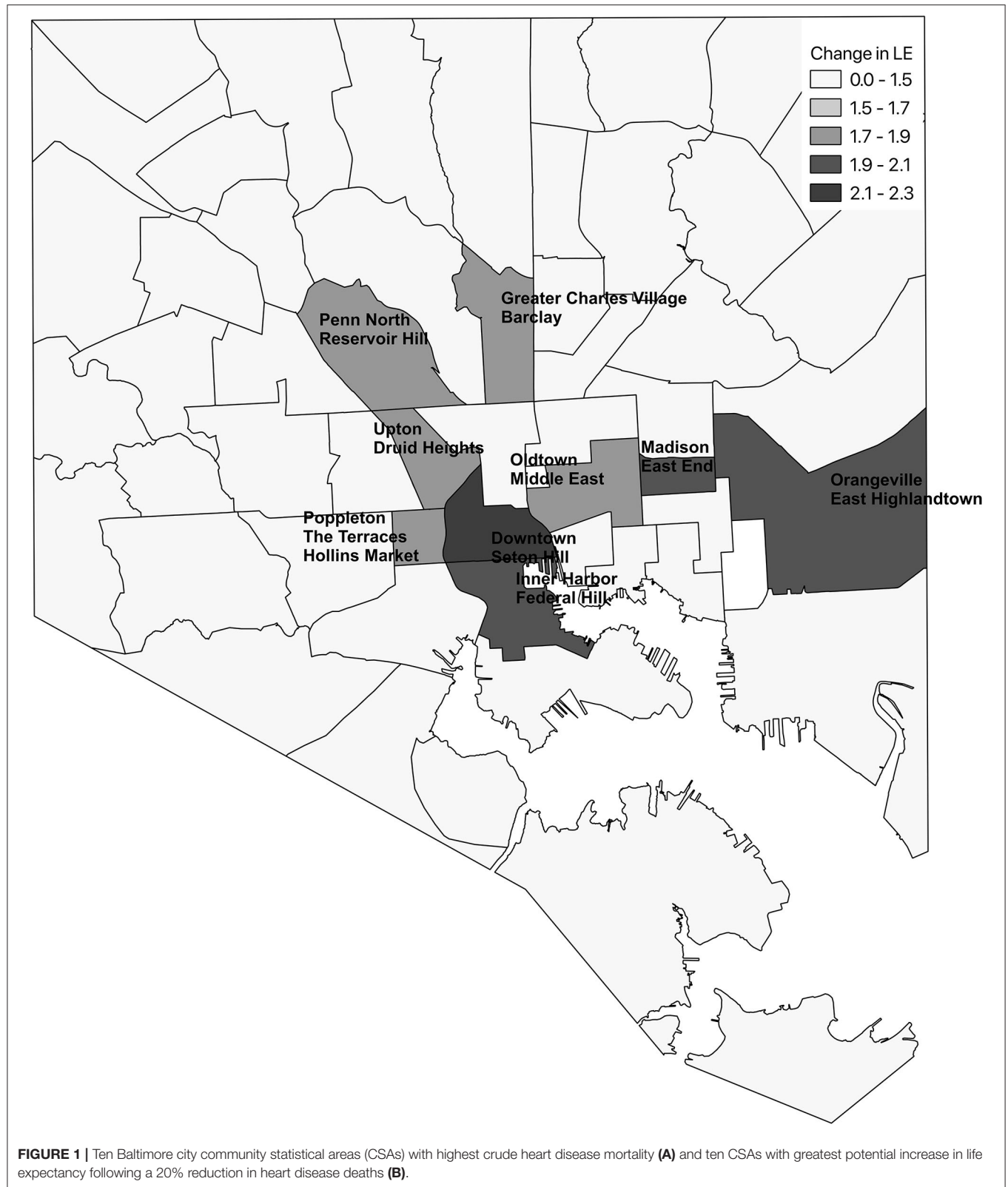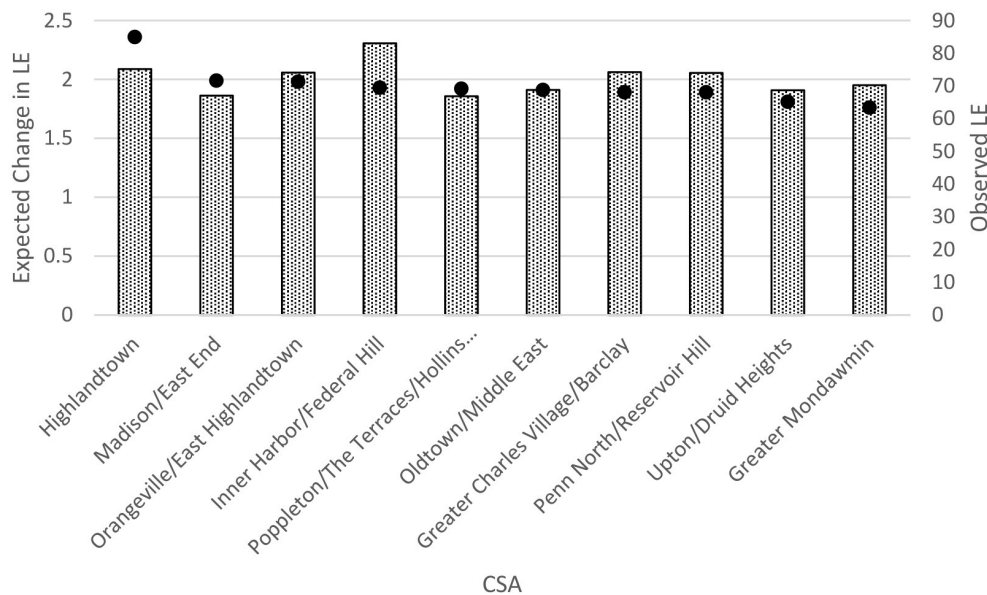
FIGURE 2 | Ten Baltimore city community statistical areas (CSAs) with greatest potential increase in life expectancy (LE) following a 20% reduction in heart disease deaths compared with observed LE in those CSAs. The bars represent the observed LEs, and the dots represent the expected change between expected LE and observed LE.

across the US [i.e., USALEEP, the US Small-area Life Expectancy Estimates Project (15)], to our knowledge this is the only tool that will then calculate potential gains in life expectancy from a measured number of lives saved. This tool allows local health decision/local government makers to quantify potential LE gains from the targeted implementation of interventions to reduce cause-specific mortality by achievable amounts.

The most notable finding from the PRLONGER tool, as demonstrated by the example of heart disease mortality reduction in Baltimore City, is that identified neighborhoods for targeted effort to reduce disease-specific risk factors might change if neighborhoods were selected based on potential LE gain as opposed to mortality burden. In terms of selecting target neighborhoods for particular disease screening or prevention efforts, different neighborhoods may emerge as having the greatest potential for LE change based on the disease of focus. This would allow local health officials to modify their work and messaging away from "blaming" the neighborhoods with highest overall mortality to instead understanding that all neighborhoods have opportunities for optimization of health and well-being for the city as a whole.

This project has several limitations. First, it is important to keep in mind that potential LE gains are heavily influenced by deaths that occur at younger ages; therefore, neighborhoods with younger age distributions, and more specifically deaths within the younger age groups, may more frequently be selected as high-impact targets for interventions. Users will need to keep in mind how the age distributions of their neighborhoods differ and interpret results accordingly. Second, the tool only considers single-causes of mortality, so neighborhoods where many younger residents are dying from a variety of causes will not emerge as areas with the highest expected LE benefits. From

a health equity perspective, this is meaningful, as these are often the most under-resourced neighborhoods, home to low-income households and people of color. Future iterations of such tools should be adapted to incorporate multiple causes of death, as well as other structural factors that may affect the predicted success rates of planned interventions. Third, we are limited by the quality of residence and cause of death coding that is available through the Vital Statistics data. Ongoing efforts should be made at every level to improve this work across the US. Finally, calculation of LE in small areas remains a challenge. In this study we aimed to align our estimates with those published by the National Center for Health Statistics. We continue to support all efforts to improve the calculation of LE in small areas.

PUBLIC HEALTH IMPLICATIONS

The PROLONGER tool can empower local health officials to quantify the potential health impacts of the focused implementation of screening and prevention efforts within their cities. Local health departments and local government could use the tool to set specific goals and justify allocation of resources, and to communicate the rationale behind their decisions to senior leadership and key stakeholders. Using such information in local decision-making may help to reduce mortality and LE inequities across the US.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: data can be obtained following review and permission from the Baltimore City Health Department.

Requests to access these datasets should be directed to Paul Overly; paul.overly@baltimorecity.gov.

AUTHOR CONTRIBUTIONS

AC conceptualized this study and oversaw all aspects of the project. CX created the tool and all code for the analysis. JG ran the code on the raw data. DP-E, SH, and KA provided valuable technical assistance throughout the process. All authors participated in the preparation of the manuscript.

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Risky Sexual Practice and Associated Factors Among Youth Preparatory Students in Gondar City, Northwest Ethiopia

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Background: Risky sexual practices can negatively affect the health of youths by predisposing them to a variety of sexually transmitted infections, including HIV/AIDS and unwanted pregnancy, which, in turn, would lead to serious lifelong deleterious health, social, and economic consequences. While youths tend to be less well-informed and require more information, little has been known in Ethiopia. Therefore, this study aimed to assess the prevalence of risky sexual practices and associated factors among youth students in Gondar city, northwest Ethiopia.

Methods: A cross-sectional study was conducted among 414 regularly attending youth students in Gondar city from April to May 2019. A simple random sampling technique was used to select the study participants. Data were collected by using a pre-tested, structured, and self-administered questionnaire. Bivariable and multivariable logistic regression analyses were employed, and a multivariable binary logistic regression model was used to identify the effect of independent variables on the outcome variable at $p < 0.05$ with its 95%CI.

Result: The prevalence of risky sexual practices was 49.3%. Peer pressure (AOR = 1.99, 95%CI: 1.21, 3.26), drinking alcohol (AOR = 4.88 95%CI: 3.06, 7.79), and watching pornography (AOR = 2.82, 95%CI: 1.74, 4.56) were positively associated with the risky sexual practice of youths. Whereas, age, gender, and pocket money did not have any association with risky sexual practice in this study.

Conclusion: In this study, the prevalence of risky sexual practices was found to be high. Thus, multisector collaboration efforts are needed from parents, schools, health facilities, and the government to tackle the exposure of in-school youth toward peer pressure, drinking alcohol, and watching pornographic films, which in turn helps to bring about healthy sexual practices among them.

Keywords: risky sexual practice, preparatory school, students, youth, Ethiopia

INTRODUCTION

Risky sexual practices are any sexual activity that increases the risk of contracting sexually transmitted infections (STI) and unintended pregnancy, which includes having sex with multiple sexual partners, early initiation of sexual intercourse under the age of 18, and not using or inconsistent use of a condom (1, 2). Based on different sources, the term youth refers to the age interval between 15 and 24 years old, and since people become sexually active at this age, a healthy sexual awareness and development class is mandatory for the future health status of the youths and adolescents in particular (3, 4).

Young people aged 10–24 years constitute around 1.8 billion and represent 27% of the world's population (5). Youths comprise one-third of Ethiopia's population, belonging to the age category of 15–24 years (6). Adolescence and youth are critical developmental periods when they begin to define and clarify their sexual values and start to experiment with sexual behaviors. Most of these youths are students, and they are also at high risk for unsafe sexual practices and problems like HIV/AIDS or STI, unwanted pregnancy, abortion, poor school performance, high school dropout rate, psycho-social problems, conduct disorder, divorce, and economic problems (7, 8).

Youths are defined as those between the ages of 15 and 24 years, which is considered a period of transition from childhood to adulthood (i.e., from the dependence of childhood to adulthood's independence) (9). They are engaged in high-risk behaviors like smoking cigarettes, drinking alcohol, use of drugs, suicide, unprotected sexual practice, unintended pregnancy, and violence (10–12). These behaviors and lifestyles learned or adopted during this period will influence health both in the present and in the future. Thus, important life-long health habits are established and carried into adulthood, in turn leading them to take part in sexual risk practices (13).

Adolescents and youths are not only a time of tremendous opportunity and change but also a time of heightened vulnerability to a variety of sexual, reproductive, social, emotional health risks including unwanted pregnancy, STI/HIV/AIDS, abortion, detachment from families, discontinuation of schooling, depression, and streetism (14). The trend of STI and HIV prevalence over time was higher in Gondar and Bahir Dar cities compared with major cities of Ethiopia (15).

Youth people's vulnerability to risky and other unhealthy behaviors is tied to a host of individual, family, and community factors that influence their behavior and that are closely related to their economic and educational opportunities (16–18).

One-third of the 340 million new STIs cases occur per year in people under 25 years of age worldwide. According to the United Nations Program on HIV/AIDS (UNAIDS), in 2008, young people aged 15–24 years accounted for 42% of new HIV infections, and nearly 80% of these individuals live in sub-Saharan Africa (19). Results from the 2015 USA national youth

Abbreviations: AIDS, Acquired Immune-Deficiency Syndrome; CSW, Commercial Sex Workers; HIV, Human Immunodeficiency Virus; RSB, risky sexual behaviors; STI, Sexually Transmitted Infections; STD: Sexually Transmitted Diseases; WHO, World Health Organization.

risky behavior surveillance system (YRBSS) indicated that many high school students are engaged in priority health-risk behaviors associated with the leading causes of death among persons aged 10–24 years. During the 12 months before the study, many high school students are engaged in sexual risk practices resulting in unintended pregnancies and STIs, including HIV infection. Nationwide, 41.2% of students had ever had sexual intercourse, 30.1% had had sexual intercourse during the 3 months before the survey, and 11.5% had had sexual intercourse with four or more persons during their life (20). In Ethiopia, a systemic review and meta-analysis study showed that the pooled prevalence of risky sexual practice was 42.80% (21).

Youth health efforts should focus on prevention since most of the disease burden is preventable, and prevention is a cost-effective strategy concerning adolescents (22). Former studies determined that chat chewing, social media, absence of interpersonal support, relationship stress, poor mother-daughter attachment, intimate partner violence, lack of religious involvement, drug and alcohol use, and treating a physical problem with prescription drugs can influence the practice of risky sexual practice of youth (21, 23–25). Local organizations have been supporting activities to increase access to sexual and reproductive health (RH) services for young people in all schools. This includes the establishment of sexual and reproductive health rights clubs in the school and the scaling-up and institutionalization of youth-friendly services through capacity building at all levels of the health system. Nevertheless, the effects of all these efforts have not been well implicit across the Ethiopian high schools and preparatory schools (26).

Preparatory school students are assets of the society and change agents in filling the gap in the past and on whom the future generation is based. It is also clear that this segment of the population is on the way to transforming into an adulthood filled with ambition and building their future academic and social career, neglecting their sexual and reproductive health can cause high social and economic costs, both immediately and in the year ahead. Existing limitations in Ethiopia were being tailored to examine the role of a single variable on the sexual behavior of youth like parenting practices, peer influence, substance use, and living arrangement separately and also being concentrated among university and college students. However, preparatory students are nested in a context where many of the aforementioned factors interact. Therefore, this study aimed to assess the prevalence of risky sexual practices and associated factors among preparatory school students in Gondar city, northwest Ethiopia.

METHODS

Study Design, Period, and Setting

A cross-sectional study was conducted from April to May 2019 in Gondar city. The city is located in Central Gondar Zone, Amhara Regional State of Ethiopia and is about 748 km northwest of Addis Ababa, the capital of Ethiopia, and about 180 kilometers from Bahir Dar city, the capital of Amhara regional state. The city has an estimated total population of 324,000. It has an altitude of $12°36'$ N $37°28'$ E and a longitude

of 12.60N 37.467'E with an elevation of 2,133 m above sea level and is divided into 12 administrative areas (sub-cities), which consist of 21 kebeles (the smallest administrative units). Gondar is among one of the ancient and largely populated cities in the country. The city has 11 governmental preparatory schools and 4 private preparatory schools. All these schools, currently providing educational services, were included in the study. This study was conducted at seven randomly selected preparatory schools (i.e., five governmental and two private).

Participants

All youths aged between 15 and 24 years who attend Gondar city preparatory schools (grades 11 and 12) were the source population and those who attended the selected schools were the study population, and students available during the data collection period were included in the study.

Inclusion and Exclusion Criteria

Those students who were available and attending class during the data collection period were included, whereas those who were seriously ill and were unable to respond and night and extension students were excluded from this study.

Sample Size Determination

The required sample size of eligible students for the study was calculated using the formula to estimate a single population proportion. The following assumptions were made to calculate the sample size: (a) A 95% probability of obtaining the population proportion of preparatory school students who experienced risky sexual practices within a 5% margin of error and (b) based on a study conducted in Ethiopia (7), the population proportion of preparatory school students who had risky sexual behaviors was assumed to be 42.8% (21).

$$n = \frac{(Z\alpha/2)^2 p(q)}{(w)^2} = \frac{(1.96)^2 * 0.428(0.572)}{(0.05)2} = 376.19 \quad (1)$$

Therefore, the required sample size was 376. Expecting a 10% non-response rate, the final sample size was calculated to be 414.

Sampling Technique and Procedure

Seven preparatory schools (i.e., five governmental and two private) were randomly selected from all 15 preparatory schools. The lists of students were obtained from each selected school registrar's office, and the sampling frame was designed by numbering the list of students. Then, the total sample size was distributed to each school based on proportional allocation to their size by using the proportional allocation formula ($ni = \frac{Ni}{N} * n$). Finally, students from each selected school in each class were selected by a simple random sampling technique using a table of random generation.

Dependent Variable

Risky sexual practices include multiple sexual partners, early initiation of sex, failure to use condoms, and sex with commercial sex workers.

Explanatory Variables

Sociodemographic variables include age, sex, religion, attending night club, watching pornographic video, psychosocial factors, the type of social media used, and substance/drug use.

Measurements

Risky sexual practices were considered as at least one of those that a student is involved in: multiple sexual partners (having more than one sexual partner until the survey), early initiation of sex (sexual debut at the age of <18 years of age), condom (inconsistent use of/failure to use the condom at least ones during sexual intercourse until the survey), sex with commercial sex workers (at least once until the survey) (27).

Early sexual initiation was defined as the experience of sexual intercourse before the age of 18 years (28).

Youth was defined as a part of the population who are in the age group of 15–24 years old (9).

Sexually active was considered for students who claimed to engage in a sexual act at least once before the study (28).

Multiple sexual partners involves having two and above sexual partners in their lifetime.

Commercial sex worker is defined as a person who works in the adult entertainment industry characterized by the provision of sexual favors for financial and non-financial rewards with a varying degree of physical contact between the parties.

Living arrangement is defined as the state of students' living with their parents, relatives, husband or wife, or others living with them.

Peer pressure, according to this study, is defined as respondents who are going to be under peer pressure if they experience any influence from their friends to have sex.

Substance use is defined as any use of at least any one of the following substances: alcohol, Chat, cigarette, Shisha, Hashish, or drugs that are assumed to affect levels of thinking and an increased risk of involving in risky sexual behavior (1).

Data Collection Procedures

A pretested and structured self-administered questionnaire was used to collect the data from the study participants. This questionnaire comprises four items namely, sociodemographic factors, psychosocial factors, type of social media users, and substance/drug use. The questionnaire was first prepared in English and then translated to the local language (i.e., Amharic) and back to English to maintain consistency of the tool. Data were collected by four diploma-holder midwives. A self-administered questionnaire was used to collect data from all selected preparatory school students who consented to be a part of the study. A one-day training was provided for the four diploma-holder midwives and one BSc midwife for supervision about techniques of data collection. The principal investigator and supervisor made day-to-day on-site supervision during the whole period of data collection and checked each questionnaire daily for completeness and consistency. The questionnaire was pre-tested to check the response, language, clarity, and appropriateness of the questionnaire while the pretest was done outside the study area with 5% of sample size, i.e., on 20 students. Based on the findings of the pre-test, modification

TABLE 1 | Sociodemographic characteristics of study participants and their parents in Gondar city, Northwest Ethiopia, 2019 (n = 414).

Variables		Frequency	Percentage
Age in years	15–18	210	50.70
	19–24	204	49.30
Sex	Male	180	43.50
	Female	234	56.50
Grade level	Grade11	245	59.20
	Grade12	169	40.80
Religion	Orthodox	308	74.40
	Muslim	63	15.20
	Protestant	37	8.90
	Catholic	6	1.50
Religious attendance	Yes	306	73.90
	No	108	26.10
Frequency Religious attendance (n = 306)	Daily	95	22.90
	Most of the time	68	16.40
	Once a week	122	29.50
	Once a month	21	5.20
Ethnicity	Amhara	347	83.80
	Tigray	26	6.30
	Qimant	26	6.30
	Oromo	13	3.10
	SNNP	2	0.50
Residence	Urban	303	73.20
	Rural	111	26.80
Marital status	Single	385	93.00
	Married	20	4.80
	Divorced	9	2.20
Living arrangement	Alone	18	4.30
	With both parents	253	61.10
	With father only	47	11.40
	With mother only	59	14.30
	Other relatives	21	5.10
	With friends	5	1.20
	With husband	5	1.20
	With wife	6	1.40
Family size	≤3	66	15.90
	4–6	253	61.20
	≥7	95	22.90
Mothers educational status	Unable to read and write	27	6.52
	Read and write	71	17.15

(Continued)

TABLE 1 | Continued

Variables		Frequency	Percentage
	Primary school	44	10.63
	Secondary	90	21.74
	Diploma	116	28.02
	Tertiary and above	66	15.94
Fathers educational status	Unable to read and write	20	4.80
	Read and write	34	8.20
	Primary school	29	7.00
	Secondary school	76	18.40
	Diploma	80	19.30
	Tertiary and above	175	42.30
Mothers occupation	Housewife	190	45.90
	Government employed	131	31.60
	Private	34	8.20
	Merchant	57	13.80
	Daily laborer	2	0.50
Fathers occupation	Government employed	186	44.90
	Private employed	82	19.80
	Merchant	108	26.10
	Farmer	31	7.50
	Daily laborer	7	1.70
Knowing Parents' average monthly income	Yes	196	47.30
	No	218	52.70
Parents average monthly income (n = 196)	<1,000	3	1.50
	1,000–2,000	20	10.20
	>2,000	173	88.30
Do you get pocket money	Yes	248	59.90
	No	166	40.10
Amount of daily pocket N = 248	≤20	149	60.08
	>20	99	39.92

of the questionnaire was done and questions were revised accordingly. The overall data collection process was supervised by the principal investigator.

Data Processing and Analysis

The data were first checked manually for completeness and then coded and entered into Epi Info version 7.1.2 (29). Then, the data were exported to Statistical Package of Social Science (SPSS) version 25 (30) for data checking, cleaning, and analysis. Descriptive statistics (like mean, standard deviation, frequencies, and percentages) were used to describe the study population about dependent and independent variables. Results were presented in text, tables, graphs, and charts.

Binary logistic regression (bivariable and multivariable logistic regression) was used to identify statistically significant independent variables, and variables having a p-value <0.2 in the bivariable analysis were entered into multivariable logistic regression for further analysis. A p-value <0.05 in the multivariable analysis was considered significant. Hosmer–Lemeshow goodness-of-fit was used to test the model fitness. Adjusted odds ratio (AOR) with a 95% confidence interval was used to identify factors associated with risky sexual practice among students.

RESULT

Sociodemographic Characteristics of the Study Participants

A total of 414 students participated with an overall response rate of %. Of these 234 (56.5%) were women. The mean age of the respondents was 19 years ± 1.61 SD. The majority, 339 (82.9%) of the study participants were orthodox by religion and 347 (83.8%) belong to Amhara ethnic group. Respondents who were living with parents account for 253 (61.1%). About, 245 (59.2%) were grade 11 students. The mean family monthly income was 4,967 ETB ± 2,206 SD (**Table 1**).

Sexual Related Characteristics of Participants

A total of 229 (55.3%) study participants have had a girlfriend or boyfriend, and out of those 117 (51.1%) have had two or more boys or girlfriends. More than half of the study participants, 216 (52.2%), had sexual intercourse ever. Of those sexually active participants, about 177 (42.8%) started sex before the age of 18 years. In this finding, 161 (38.9%) of the study participants reported that they have had the first sexual intercourse with their boyfriend and or girlfriend. About 91 (35.8%) of the study participants reported to have had sex with personal desire (**Table 2**).

Psychological and Social Media Related Characteristics of Study Participants

In total, 155 (37.4%) study participants have experienced peer pressure to have had sex, while 208 (50.2%) participants have reported their best friends have had sex. The majority of the students, 370 (89.4%), have used social media, with telegram being used dominantly by 264 of them (35.9%) (**Table 3**).

Prevalence of Risky Sexual Practices

In this study, the risky sexual practices were assessed by variables like number of multiple sexual partners, age at first sex, condom use, and sex with commercial sex workers. Thus, the prevalence of risky sexual practices among preparatory school students in Gondar city was 49.3% (95%CI: 46.4%−55.6%). Male students were highly (57.8%) engaged in risky sexual practices. This study illustrated that 52.2% of the study participants are sexually active, with 43.2% having sex 12 months before this data collection period. The predominant reason for initiation of sex was being under the influence of alcohol followed by peer pressure (**Figure 1**).

Factors Associated With Risky Sexual Practices

On bivariable analysis, variables that were found to have an association with risky sexual practices were daily pocket money, peer pressure, drinking alcohol, and watching pornography. A multivariable analysis was also done to identify the independent effect of the variables by controlling the confounding effect of other variables (31). Accordingly, three variables were found to have a significant association with risky sexual behaviors at a p-value <0.05. These include consuming alcohol, experiencing peer pressure to have sex, and watching pornography.

The odds of having risky sexual practices among students experiencing peer pressure to have sex was nearly two times higher than those who did not experience such pressure from their peers (AOR = 1.99; 95%CI: 1.21–3.26). Moreover, this study has also revealed that exposure to pornographic movies puts the students at higher risk of practicing risky sexual practices. Students who watched pornographic movies had 2.82 times higher odds of undertaking risky sexual practices than their counterparts who did not watch pornographic movies (AOR = 2.82; 95%CI: 1.74–4.56).

This study further declared that students who have reported drinking alcohol were 4.88 times more likely to engage in risky sexual practices as compared to their counterparts who did not drink alcohol (AOR = 4.88; 95%CI: 3.06–7.79) (**Table 4**).

DISCUSSION

We have conducted this study to determine the prevalence of risky sexual practices and factors associated with them among Gondar city preparatory school students. Accordingly, our study illustrated that the proportion of respondents who engaged in risky sexual practices was 49.3 % (95%CI: 46.4–55.6). The key findings of this study point out the role of social determinants of health in risky sexual practice in youths and the necessity of conducting further qualitative research to address behavioral-related social determinants of health in the context of sexuality. The findings also underpin the need for considering the results when developing and implementing strategies to improve the sexual behavior of youths as they do not usually get the right information, good overall care, and enough consultation time.

TABLE 2 | Sexual practice-related characteristics of study participants in Gondar city, Northwest Ethiopia, 2019 (*n* = 414).

Variables		Frequency	Percentage
Having a girl/boyfriend	Yes	229	55.30
	No	185	44.70
Number of girl/boyfriend (*n* = 229)	1	112	48.90
	≥2	117	51.10
Having started sexual intercourse	Yes	216	52.20
	No	198	47.80
Age of 1st sex (*n* = 216)	<18	177	81.90
	18–24	39	18.10
Age of 1st sex with a sexual partner (*n* = 216)	Younger	30	13.90
	Older	77	35.60
	Equal age	16	7.40
	Don't know	93	43.10
With whom having sex with (*n* = 216)	Boy or girlfriend	161	74.50
	Commercial sex workers	15	6.90
	Unknown person	32	14.80
	Relatives	8	3.80
Reason to start sex (*n* = 216)	Personal desire	91	35.83
	Peer pressure	63	24.80
	Influence of alcohol	61	24.02
	Influence of chat or drug	6	2.36
	Economic problem	22	8.66
	Rape	11	4.33
Number of partners having sex with (*n* = 216)	Only one	129	60.00
	Two or more	70	32.60
	Don't remember	17	7.40
Number of intimate friends in the last 12 months	Only one	131	31.60
	Two or more	199	48.10
	Don't have	84	20.30
Sexual contact in the last 12 month	Yes	179	43.20
	No	235	56.80
Using condom during sex (*n* = 216)	Yes	127	41.00
	No	89	59.00
Frequency of using condom(*n* = 127)	Always	42	33.10
	Rarely	85	66.90
Substance usage	Yes	96	23.20
	No	318	76.80
Types of substances used (*N* = 96)	Chat	53	48.62
	Cigarettes	22	20.18
	Hashish	32	29.36
	Weeds	2	1.83
Usage of alcohol	Yes	211	51.00
	No	203	49.00
Frequency of alcohol usage (*n* = 211)	Always	22	10.43
	Some times	120	56.87
	Only on holidays	69	32.70
Enjoy night clubs	Yes	154	37.20
	No	260	62.80
Frequency of enjoying nightclubs (*n* = 154)	Daily	3	1.95
	Every weekend	44	28.57
	At least twice a week	26	16.88
	At least once a month	81	52.60
Sex with CSW (*n* = 124)	Yes	93	75.00
	No	31	25.00
Sexually transmitted infection (*n* = 216)	Yes	26	12.00
	No	190	88.00

TABLE 3 | Psychological and social media-related characteristics of study participants in Gondar city, Northwest Ethiopia, 2019 (*n* = 414).

Variables		Frequency	Percentage
Peer pressure	Yes	155	37.40
	No	259	62.60
Best friends have had sex	Yes	148	35.80
	No	208	50.20
	Don't know	58	14.00
Number of friends who have had sex	All	76	18.40
	None	157	37.90
	Don't know	181	43.70
Academic performance	Excellent	149	36.00
	Good	214	51.70
	Poor	51	12.30
Social media used	Yes	370	89.40
	No	44	10.60
Frequency of social media used	Daily	132	35.68
	Often	97	26.22
	Occasionally	80	21.61
	Rarely	61	16.49
Type of social media used*	Facebook	242	32.88
	Telegram	264	35.87
	Instagram	114	15.49
	Viber	84	11.41
	IMO	27	3.67
	Whats up	5	0.68
Watching pornography	Yes	185	44.70
	No	229	55.30
Frequency of watching pornography	Daily	32	17.30
	Often	27	14.60
	Occasionally	46	24.90
	Rarely	80	43.20
With whom watching pornography	Alone	126	68.10
	Boy or girlfriend	50	27.00
	Family members	4	2.20
	Unknown person	5	2.70
What do you feel about risky sexual behavior??	It is bad	143	34.50
	It hurts us	77	18.60
	Don't know	194	46.90
Having risky sexual behavior	Yes	204	49.30
	No	210	50.70

More than one response noted.

Accordingly, this finding is in line with a study conducted in Lalibela town (46.5%) (1). This similarity might be due to geographical as well as cultural closeness between the two study areas; as a result, the population's attitude toward having sex and taking safety measures would be equally affected while it is lower than a study conducted on students of Debre Markos University (58.15%) (19) and by the National Adolescent and Youth Health Strategy (2016–2020) (32). The possible difference observed might be because of the difference in educational level, living arrangement, study area, sample size differences, and unpredictability behaviors of sexual practices of youths.

On the other hand, the prevalence of risky sexual practices in this study is much higher compared to a study conducted in Gondar city administration where the overall prevalence of risky sexual practices was 12.8% (26), in Arsi Negelle was 32% (33), in Axum was 19% (3), in Wolaita Sodo was 24.7% (12), and in Humera was 13.7% (34). This variation among reports might be due to differences in the difference in grade level since our study participants are higher grade students (preparatory students) compared to the previous two studies conducted among high school students so that higher grade students had more exposure to risky sexual practices than junior high school students. Since they consider themselves to be in place to practice everything,

they are much more eager to test their sexual ability than those in the lower classes.

Turning to the associated factors, respondents who watched the pornographic films were at higher risk to engage in risky sexual practice with an odds ratio of 2.82 (AOR = 2.82; 95%CI: 1.74–4.56). This may be due to the access to enhanced mobile technology, the internet, and widespread porn video media portrayals across every corner of the world which fuels the problem of risky sexual practice among youths. Regarding this, youths are highly addicted to the usage of more advanced technologies that pave the way for watching these pornographic videos that initiate them to practice without thinking about the consequences. Furthermore, youths are eager and sensitive to experiment with what they hear and look at those videos; since they are at the natural transition stage to adults and hence, they are prone to be driven by porn videos they watch to experiment with risky sex. This finding is consistent with studies in Gondar (26), Haramaya (35), Humera (34), Arba Minch (10), xum (3), Nekemte (36), and Jimma (37).
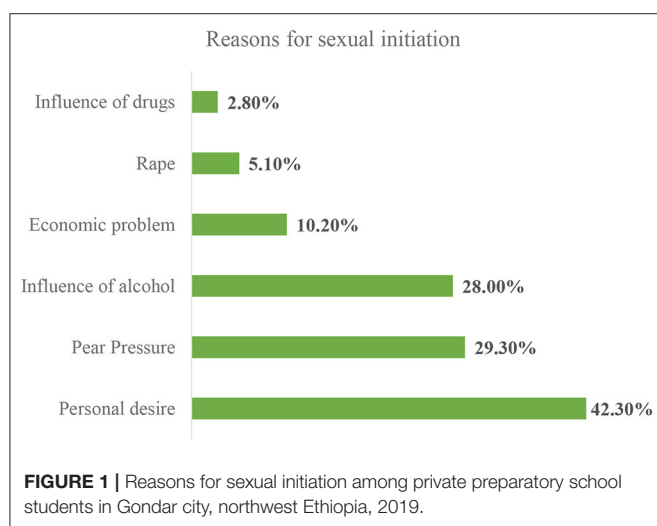
Furthermore, this study has also indicated that respondents who drink alcohol were 4.88 times (AOR = 4.88; 95%CI: 3.06–7.79) at higher risk to involve in risky sexual practices. This may be a result of the myopic effect of alcohol to make a rational decision by considering the consequence of risky sexual behavior. Individuals with alcohol influence deciding without analyzing consequences to be followed after having sex and drinking alcohol is one of the driving factors for individuals to engage in unprotected sex (inconsistent use of a condom), sex with commercial sex workers, and sex with an unknown person (multiple sexual partners) and might result in STI including HIV and unwanted pregnancy in case of women, which are all indicators of risky sexual behavior. Similar findings were also observed in studies conducted in Ethiopia (11, 38, 39), Kenya (40), and Saudi (41).

Lastly, respondents who experienced peer pressure to have sex were 1.99 times (AOR = 1.99; 95%CI: 1.21–3.26) more at risk of risky sexual practices than their counterparts. A plausible explanation is that, since youth spend most of their time with their peers, peers are the most influential socializing agent for sexuality among youths. As youths need attention and recognition from peers, they are liable to behave in a manner their intimate friend practices. So, if they have a sexually active friend that provoke them to involve in such a way, they will be in danger of committing unhealthy sexual behaviors the same way their friends do. This finding is supported by studies conducted in Gondar (26), Lalibela (6), Arsi Negelle (33), and Jimma (42).

In our study, factors such as age, sex, religious attendance, residence, living arrangement, parental educational status, having a girlfriend or boyfriend, having started sex, age of first sex, and enjoying nightclubs had not had a significant association with risky sexual behavior. Studies revealed that being in the age group 21–23 (43), being a woman (37), urban residence (1), and enjoying nightclubs (44) had its effect by increasing the likelihood of risky sexual behavior. While regular religious attendance and living with parents protect students from those risky sexual practices (34), not having such a significant association in our study in contrary with the other findings might be because of differences in the educational level of participants, sample

FIGURE 1 | Reasons for sexual initiation among private preparatory school students in Gondar city, northwest Ethiopia, 2019.

TABLE 4 | Bivariable and multivariable logistic regression analysis of factors associated with risky sexual practice among preparatory school students, in Gondar city, northwest Ethiopia, 2019.

Variables		Risky sexual Practice		COR 95%CI	AOR 95%CI
		Yes	No		
Get daily pocket money	Yes	142	106	2.24 (1.5–3.36)	1.54 (0.96–2.47)
	No	62	104	1	
Drinking alcohol	Yes	152	59	7.48 (4.84–11.56)	4.88 (3.06–7.79)**
	No	52	151	1	
Peer pressure	Yes	107	48	3.72 (2.44–5.69)	1.99 (1.21–3.26)*
	No	97	162	1	
Watching pornography	Yes	130	55	2.8 (1.25–4.53)	2.82 (1.74–4.56)**
	No	105	124	1	

*1, Reference category, **Significant at p ≤ 0.001,*Significant at p < 0.05.*

size, the year difference the studies conducted, and because of unpredictability behaviors of sexual practices of youths.

Limitations of the Study

Despite the self-administered data collection method, due to the sensitivity of the topic itself, social desirability bias may be introduced, which can lead to underestimating the prevalence of risky sexual practices among in-school youth students. In addition, due to the nature of the study design, it may not show causation. This study is not triangulated with a qualitative study design, which is better in in-school youths describing their life experiences and behavioral factors. Finally, since the study was conducted in a single city, it could not be generalized to the rest of the country.

Implications of the Study

The evidence from this study calls upon policymakers, program managers, researchers, school administration, parents, and communities to play a role in preventing risky sexual behaviors and their consequences through, information, education, counseling provision, community mobilization, and integration of behavioral, social, policy, structural, or other interventions.

CONCLUSION

The findings of this study strongly indicated that the prevalence of risky sexual practices among school youths in Gondar city, Ethiopia is quite common. Factors like ever using alcohol, ever watching pornographic videos, and peer pressure to have sex were important factors for increasing the magnitude of risky sexual behaviors among in-school youths. Thus, collaborative efforts are needed from parents, schools, health facilities, and the government to mitigate the exposure of in-school youths toward peer pressure, drinking alcohol, and watching pornographic films

which in turn helps to bring about healthy sexual behaviors among them.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Gondar Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

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Knowledge and Response to Stroke Among Lebanese Adults: A Population-Based Survey

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Objectives: To date, research on public awareness of stroke warning symptoms, risk factors and practice in the general adult population in Lebanon is scarce. The aim of our study is to identify the level of stroke awareness in order to develop and implement preventive measures particularly in relationship to primary stroke prevention.

Methods: It is a cross-sectional study conducted among 410 adult participants from the five main governorates of Lebanon. Stroke knowledge and practice were assessed using two validated questionnaires namely the Stroke Knowledge Test (SKT) and the Stroke Action Test (STAT). Multivariable linear regression models were conducted to examine socio-demographic, social habits, and clinical factors independently associated with the SKT and the STAT scores.

Results: The mean SKT score of the participants was 9.16. 48.5% showed a poor stroke-related knowledge level and 51.5% a good knowledge level. Living in Mount Lebanon and occasional smokers showed statistically significant lower mean SKT scores; whereas, university degree and suffering from diabetes mellitus were associated with higher mean SKT scores. The mean overall STAT score was 41.3%. For 36.8% of the stroke symptoms, respondents selected call 112. The mean STAT scores of participants who get their information from the internet was statistically significantly lower. However, no association was found between the SKT score and the STAT score.

Conclusion: Knowledge of stroke risk factors was low, as was awareness of the need to call 112 in response to stroke symptoms. Hence, it is essential to develop health education programs in order to decrease stroke morbidity and mortality.

Keywords: stroke, awareness, knowledge, practice, Lebanon

INTRODUCTION

Globally, stroke is a primary cause of mortality and morbidity that results in high disability rates (1–4). Age, positive family history, chronic conditions such as diabetes, hypertension, and cardiovascular diseases are common risk factors of stroke. In addition, certain lifestyle habits including smoking and alcohol intake are also known stroke risk factors (5, 6). It is

well-documented that 80% of stroke cases can be prevented through lifestyle changes and control of modifiable risk factors (3, 4), hence emphasizing the importance of primary prevention.

Over the years, the burden of stroke increased, its incidence has escalated in low and middle-income countries; while it declined in high-income countries to 42% (7–9). Regarding the Middle East, among the developing countries, the World Bank reported that stroke incidence rates have significantly increased over the last decade; they ranged from 22.7 to 250 per 100 000 per year in 2000–2014 compared to the gross rates of 112–223 per 100 000 per year in 2000–2008 among the high-income countries (10). Lebanon, a small country located in the Middle East on the eastern shore of the Mediterranean Sea, lacks data on stroke prevalence. According to the WHO, stroke is the second leading cause of mortality in Lebanon with 9.4% of all deaths in 2012. Furthermore, a study conducted in 2015 showed an adjusted prevalence of stroke of 0.5% and a world standardized prevalence of 0.6% in Lebanon which is higher than other emerging countries in the Middle East (11). It is noteworthy to mention that the prevalence of risk factors of stroke such as smoking, obesity, low physical activity, and hypertension is high in the Lebanese community (12, 13). In addition, Farah *etal*. reported that 1 out of 8 Lebanese residents without prior stroke or TIA experienced stroke symptoms and a positive association between stroke risk factors and stroke symptoms prevalence was seen (14). According to the World Economic Forum, Lebanon is ranked globally as the 10th best overall for quality education with a literacy rate of 93.9% (15). In 2012, a net enrolment rate of 93.3% was recorded in primary education and 46.3% in higher education (16). This is attributed to the limited availability of public higher education, with only one public university in the country. Nevertheless, because of the current economic and financial crisis in Lebanon, the rising tuition fees in private schools and universities is expected to negatively affect the affordability of education to low-income households.

Early hospitalization and timely treatment could prevent the high morbidity and mortality in stroke (17–19) but delay often occurs due to lack of knowledge about warning signs of stroke, poor infrastructure, and indecision about hospital admission despite the availability of appropriate infrastructure and facilities (20). Moreover, there is a lack of awareness that timely treatment of comorbidities and proper lifestyle modifications may reduce stroke occurrence as well as morbidity among survivors of stroke (21). Thus, preventative measures are warranted particularly regarding primary stroke prevention.

Worldwide, former studies have shown poor knowledge of stroke symptoms and risk factors in the general public (22–33). According to studies conducted in Jordan (34), in Uganda (35), and in Egypt (29), 47, 75, and 68.2% of the subjects couldn't identify any stroke risk factor, respectively. Moreover, Alreshidi et al. revealed that the majority of the Saudi population showed poor stroke risk factors and warning signs knowledge leading to insufficient KAP in 63.8% of the participants (36). Consequently, in primary stroke prevention, awareness is the first approach to diminish stroke incidence in the general public (37–41). Knowledge of stroke risk factors and warning signs is necessary

in stroke prevention as well as the readiness in implementing prevention measures (37–42).

To date, research on public awareness of stroke warning symptoms, risk factors and practice in the general adult population in Lebanon is scarce. Therefore, a community-based survey aimed to evaluate the knowledge and response of Lebanese adults toward stroke is of outmost importance in order to identify the level of stroke awareness in order to develop and implement preventive measures particularly in relationship to primary stroke prevention.

METHODS

Study Design and Sampling

A total of 410 participants were recruited randomly from the five main governorates of Lebanon between the months of February and August 2020. These include Beirut, Mount Lebanon, North, South and Bekaa. The regions of Mount Lebanon and Beirut share the highest number of inhabitants- around 75%- according to national registries.

In this cross-sectional study, participants were first given a brief explanation of the study, and consent was obtained upon filling a self-administered questionnaire. Due to the COVID-19 situation, it was modified to a google form survey in order to be able to proceed with data collection. According to the Epi info sample size calculations, providing a confidence level of 95%, a margin of error of 5%, and assuming 36% of the population have adequate KAP according to a study conducted in Saudi-Arabia (36), a total sample of 354 Lebanese adults were targeted.

Lebanese adults aged 18 years and over were included in the study. Participants under 18 or who do not hold a Lebanese nationality were excluded.

Review board approval was acquired on the 5th of October 2019 from the Lebanese University.

Questionnaire

The instrument used was adopted from two validated and reliable stroke questionnaires namely the Stroke Knowledge Test (SKT) that has a validated Arabic version and the Stroke Action Test (STAT) which was translated into Arabic. The SKT and the STAT aimed at evaluating the participant's knowledge and practice toward stroke, respectively. The survey instrument was then piloted on 10 subjects prior to its finalization and distribution. The questionnaire's final version included 3 sections.

The first section was concerned with the respondents' socio-demographic characteristics, social factors and habits, family history, and medical profile. Registered data included age, gender, marital status, education level, social security insurance, occupation; whether they have ever known anyone who has ever had a stroke, where they get their health information. Presence of known stroke risk factors such as alcohol consumption, smoking, dyslipidemia, diabetes, hypertension, abnormal heart rhythm, previous cerebrovascular disease, previous MI, family history of cardiovascular or cerebrovascular disease.

The second part investigated the knowledge of stroke, risk factors and warning signs of stroke using the SKT.

TABLE 1 | Bivariate analysis of factors associated with the SKT.

Social and demographic data

Variable	Mean ± SD
Gender	
Male	48.92 ± 23.476
Female	46.60 ± 23.538
p-value	0.32
Age	
18-44	49.86 ± 22.286
45 and above	43.87 ± 25.281
p-value	0.018
Patient's marital status	
Single	49.31 ± 22.685
Married	46.88 ± 24.247
Divorced	42.87 ± 21.916
p-value	0.437
Patient's level of education	
Primary/complementary education (Elementary)	50.91 ± 31.363
Secondary education (high school)	63.07 ± 20.232
Universal education	45.81 ± 22.988
p-value	<0.001
Work status	
Person without any professional activity (I don't work)	48.22 ± 21.532
Worker	48.38 ± 23.653
Unemployed	43.14 ± 25.439
Retired	47.17 ± 24.828
p-value	0.660
Does the patient have social security insurance?	
No	43.42 ± 25.326
Yes	50.848 ± 21.684
p-value	0.002
Region/Governorate	
Beirut	44.87 ± 25.157
Mount Lebanon	42.82 ± 22.812
Other	52.89 ± 22.611
p-value	<0.0001
Current smoking	
Every day	43.91 ± 24.896
Occasionally	53.62 ± 21.402
Never	46.99 ± 23.424
p-value	0.015
Have you ever smoked at least 100 cigarettes throughout your life? [5 packages = 100 cigarettes]	
Yes	44.50 ± 23.528
No	48.96 ± 23.426
p-value	0.091
Daily alcohol consumption	
Occasionally	45.88 ± 23.088
Never	50.81 ± 23.595
p-value	0.035
Has any family member or close friend suffered a stroke?	
No	47.45 ± 23.792

(Continued)

TABLE 1 | Continued

Social and demographic data

Variable	Mean ± SD
Yes	48.24 ± 23.194
p-value	0.736
Family history of Heart failure	
No	47.27 ± 23.447
Yes	51.49 ± 23.677
Don't know	47.76 ± 23.893
p-value	0.530
Family history of Stroke	
No	46.80 ± 23.829
Yes	49.35 ± 22.042
Don't know	55.54 ± 21.208
p-value	0.112
Family history of myocardial infarction	
No	47.32 ± 24.027
Yes	47.60 ± 23.924
Don't know	51.26 ± 18.448
p-value	0.633
Family history of atrial fibrillation	
No	45.63 ± 23.768
Yes	50.47 ± 23.701
Don't know	48.73 ± 22.047
p-value	0.165
Have you ever had/Do you have Stroke? If yes, was this in the last 12 months?	
No	47.72 ± 23.553
Yes	50.19 ± 22.721
p-value	0.718
Have you ever had/Do you have Heart Attack ? If yes, was this in the last 12 months?	
No	47.32 ± 23.462
Yes	53.71 ± 23.639
p-value	0.149
Have you ever had/Do you have Angina? If yes, was this in the last 12 months?	
No	47.95 ± 23.462
Yes, in the last 12 months	44.88 ± 24.775
p-value	0.567
Have you ever had/Do you have transient ischaemic attack (TIA)? If yes, was this in the last 12 months?	
No	47.55 ± 23.589
Yes	57.95 ± 17.912
p-value	0.171
Have you ever had/Do you have diabetes? If yes, was this in the last 12 months?	
No	47.29 ± 23.592
Yes, in the last 12 months	39.55 ± 24.533
Yes, long ago	59.55 ± 17.719
p-value	0.007
Have you ever been told by a doctor that you have high blood pressure?	
No	47.57 ± 23.286

(Continued)

TABLE 1 | Continued

Social and demographic data

Variable	Mean ± SD
Yes, but without medication	49.39 ± 23.553
Yes, with medication	48.66 ± 25.309
p-value	0.923
Have you ever been told by a doctor that you have high cholesterol?	
No	49.65 ± 22.577
Yes, but without medication	41.11 ± 27.783
Yes, with medication	39.94 ± 23.593
p-value	0.007
Have you ever been told by a doctor that you have abnormal heart rhythm (atrial fibrillation)?	
No	48.27 ± 23.330
Yes, but without medication	46.24 ± 27.607
Yes, with medication	41.11 ± 23.365
p-value	0.400
Where do you get most of your health information? Internet	
No	51.80 ± 22.803
Yes	45.85 ± 23.636
p-value	0.016
Where do you get most of your health information? Newspaper/Magazine	
No	47.04 ± 23.957
Yes	52.81 ± 19.724
p-value	0.056
Where do you get most of your health information? Television	
No	46.42 ± 23.393
Yes	51.53 ± 23.513
p-value	0.051
Where do you get most of your health information? Health/fitness center	
No	47.93 ± 23.391
Yes	46.22 ± 25.086
p-value	0.686
Where do you get most of your health information? Friends	
No	47.43 ± 23.462
Yes	49.06 ± 23.742
p-value	0.556
Where do you get most of your health information? Church	
Yes	47.70 ± 23.544
No	58.69 ± 17.925
p-value	0.374
Where do you get most of your health information? Alternative practitioners	
No	47.52 ± 23.536
Yes	55.92 ± 21.878
p-value	0.201
Where do you get most of your health information? Nurse	
No	47.50 ± 23.687
Yes	50.25 ± 22.056
p-value	0.463

(Continued)

TABLE 1 | Continued

Social and demographic data

Variable	Mean ± SD
Where do you get most of your health information? Doctor	
No	47.15 ± 23.969
Yes	48.30 ± 23.176
p-value	0.625
Where do you get most of your health information? Family member	
No	47.57 ± 23.298
Yes	48.75 ± 24.512
p-value	0.693
Where do you get most of your health information? Don't know	
No	47.90 ± 23.681
Yes	46.57 ± 21.699
p-value	0.757

The SKT is a 20-items questionnaire developed by Sullivan and Dunton (43). The cut off point for good knowledge level is 50% of the 20 items. The tool has demonstrated good internal consistency, test-retest reliability and construct validity (25, 43).

Results from psychometric investigations were established at Cronbach of 0.65 in the original questionnaire demonstrating its reliability and validity in stroke knowledge assessment (43). The instrument is used worldwide and has been translated into other languages including Arabic by Eshah (34) in her study entitled "Knowledge of Stroke and Cerebrovascular Risk Factors in Jordanian adults". For the Arabic version, face and content validity were established with a Cronbach's alpha of 0.68 (34). A copy of the tool in both versions with the answers were obtained by directly contacting Dr. Sullivan and Pr. Eshah through email and permission to use the tool was granted. Minor adjustments were made to the Arabic version by changing certain terminologies as dialects differ in different Arabic countries (44).

Reliability of the instrument in our study was established with a Cronbach alpha of 0.877.

The last part of the survey explored appropriate practice toward stroke using the STAT. It is a 21 items questionnaire developed by Billings-Gagliardi and Mazor (45) in the study entitled "Development and Validation of the Stroke Action Test." The objective of the study was to develop and assess a tool where the participant needs to link individual stroke and non-stroke symptoms with the most appropriate action. The reliability of the 28-item test was good as determined by a Cronbach's alpha of 0.83 (45).

A copy of the STAT tool was obtained by contacting Dr. Billings-Gagliardi directly by email and permission to use the tool granted. The instrument was translated to Arabic by two bilingual experts and back translation into English was performed by two additional bilingual experts. The language experts compared the original English instrument with the back translated Arabic instrument and edited to obtain the matched Arabic version.

TABLE 2 | Multivariate analysis taking the SKT as the dependent variable.

Linear regression taking the SKT as the dependent variable

Variable	Unstandardized beta	Standardized beta	*p*-value	Confidence interval	
Region-ML/Beirut*	−8.819	−0.190	<0.001	−13.195	−4.443
Education-secondary/University*	7.217	0.133	0.006	2.091	12.343
Current smoking: occasionally/No smoking*	−13.099	−0.116	0.016	−23.708	−2.489
Medical history of diabetes-yes long ago/None*	12.719	0.124	0.010	3.045	22.393

Reference group.

Reliability of the instrument in our study was established with a Cronbach alpha of 0.923.

Data Analysis

Statistical analyses were performed using Statistical Package for Social Science (SPSS) version 23 (IBM SPSS Software, Chicago, IL, USA). Descriptive statistics were calculated using mean and standard deviation for continuous measures, counts and percentages for categorical variables.

A reliability test was performed for each of the questionnaires used using Cronbach's alpha to determine internal consistency. Data was weighted according to age and gender. The assumptions of the statistical tests were checked. The Student *t*-test and ANOVA test were used to assess the association between each continuous independent variable (knowledge: SKT score, and practice scores) and the sociodemographic variables. Multivariable linear regression models were conducted to examine factors associated with the SKT and the STAT scores as dependent variables and taking all variables that showed a $p < 0.25$ (46) in the bivariate analysis as independent variables. A two-sided $p < 0.05$ was used to indicate statistical significance.

RESULTS

Socio-Demographic Characteristics and Clinical Profile

A total of 410 participants from the 5 districts of Lebanon completed the questionnaire. The respondents' socio-demographic characteristics, social factors and habits, family history and medical profile are summarized in Table 1 in **Appendix A**.

The study population included 281 women (68.5%) and 129 males (31.5%), with 77.6% aged between 18 and 44 and 22.4% aged 45 and above. The results showed that 48% of the subjects were married, 37.3% without any professional activity, 62% with social security insurance and 89% had completed a university degree. In addition, the majority of participants (48%) lived in Mount Lebanon and 20.2% in Beirut. 23.7 and 55.9% of the respondents were occasional smokers and alcohol consumers, respectively. Around 45% of the participants had a family member or a friend who suffered a stroke.

Of the 410 respondents, many modifiable stroke risk factors were observed. The most prevalent were diabetes (89%) and dyslipidemia (86.9%) followed by hypertension (63.8%) and atrial fibrillation (49.4%). Moreover, 29.7% declared getting their health information from television and 22.6% from a health or fitness center.

Knowledge of Stroke

The mean SKT score of the participants was 9.16. Respondents were divided into 2 groups based on their SKT scores. 48.5% ($n = 199$) scored <50% and therefore showed a poor stroke-related knowledge level and 51.5% (211) a good knowledge level.

In addition, 61% of the sample was able to identify the pathological mechanism of stroke.

Moreover, of the 8 modifiable risk factors considered, the average score for knowledge was 3.49 of 8. 12.4% of participants were not able to identify 1 risk factor, around 20% were able to recognize 4 and approximately 43% were unable to enumerate more than 3. The most frequently recognized risk factors were physical inactivity (70.5%), obesity (69.3%), and hyperlipidemia (67.3%) followed by hypertension (52.9%).

In the bivariate analysis, being between 18 and 44 years old ($p = 0.018$), having a university degree compared with secondary education ($p < 0.001$), social security insurance ($p = 0.02$) and a medical history of diabetes mellitus ($p = 0.07$) were significantly associated with a higher SKT score. On the other hand, the mean SKT scores of participants living in Mount Lebanon compared with Beirut ($p < 0.0001$), who are occasional smokers vs. non-smokers ($p = 0.015$), occasional alcohol drinkers compared with non-drinkers ($p = 0.035$), who have a medical history of hyperlipidemia ($p = 0.007$) and who get their health information form the internet ($p = 0.016$) were significantly lower (**Table 1**).

In the multivariate linear regression, living in Mount Lebanon compared with Beirut (ß = −8.819, $p < 0.001$) and occasional smokers compared with non-smokers (ß = −13.099, $p = 0.016$) showed statistically significant lower mean SKT scores; whereas, university degree vs. secondary education (ß = 7.217, $p = 0.006$) and suffering from diabetes mellitus (ß = 12.719, $p = 0.01$) were associated with higher mean SKT scores (**Table 2**).

Response to Stroke

The mean overall STAT score was 41.3%. On average, for 36.8% of the stroke symptoms, respondents selected call 112. Moreover, of the 21 stroke symptoms considered, ~41.5% of respondents were unable to identify the most appropriate action to more than 6 stroke symptoms and around 14% responded correctly to all symptoms.

The stroke symptoms for which the fewest percentage of respondents would call 112 were "sudden loss of coordination" (0.7%), followed by "sudden confusion" (24.6%), "sudden

TABLE 3 | Bivariate analysis of factors associated with STAT score.

Social and demographic data

Variable	Mean ± SD
Gender	
Male	43.64 ± 26.550
Female	41.15 ± 23.531
p-value	0.316
Age	
18–44	42.44 ± 24.577
45 and above	42.19 ± 25.977
p-value	0.924
Patient's marital status	
Single	43.74 ± 24.026
Married	40.86 ± 26.005
Divorced	48.67 ± 21.198
p-value	0.335
Patient's level of education	
Primary/complementary education (Elementary)	57.33 ± 21.405
Secondary education (high school)	39.10 ± 30.207
University education	42.17 ± 24.324
p-value	0.096
Work status	
Person without any professional activity (I don't work)	40.62 ± 24.547
Worker	43.88 ± 25.422
Unemployed	39.33 ± 22.098
Retired	37.40 ± 25.771
p-value	0.361
Does the patient have social security insurance?	
No	41.65 ± 24.648
Yes	43.37 ± 25.625
p-value	0.492
Region/Governorate	
Beirut	38.94 ± 24.048
Mount Lebanon	43.28 ± 23.776
Other	42.62 ± 26.378
p-value	0.514
Current smoking	
Every day	41.85 ± 26.916
Occasionally	43.59 ± 24.453
Never	42.06 ± 24.605
p-value	0.865
Have you ever smoked at least 100 cigarettes throughout your life? [5 packages = 100 cigarettes]	
Yes	44.79 ± 27.637
No	41.49 ± 24.040
p-value	0.275
Daily alcohol consumption	
Occasionally	42.48 ± 25.973
Never	42.33 ± 23.749
p-value	0.954
Has any family member or close friend suffered a stroke?	
No	41.03 ± 24.058

(Continued)

TABLE 3 | Continued

Social and demographic data

Variable	Mean ± SD
Yes	43.39 ± 25.783
p-value	0.345
Family history of heart failure	
No	41.76 ± 24.997
Yes	48.51 ± 26.259
Don't know	40.59 ± 23.861
p-value	0.207
Family history of stroke	
No	42.97 ± 25.554
Yes	38.94 ± 20.537
Don't know	41.04 ± 25.866
p-value	0.559
Family history of myocardial infarction	
No	42.80 ± 26.126
Yes	42.19 ± 23.202
Don't know	40.50 ± 26.811
p-value	0.869
Family history of atrial fibrillation	
No	41.75 ± 26.409
Yes	45.21 ± 23.601
Don't know	38.52 ± 23.388
p-value	0.168
Have you ever had/Do you have stroke? If yes, was this in the last 12 months?	
No	42.32 ± 25.206
Yes	43.64 ± 19.508
p-value	0.856
Have you ever had/Do you have heart attack ? If yes, was this in the last 12 months?	
No	41.58 ± 25.200
Yes	52.04 ± 20.937
p-value	0.026
Have you ever had/Do you have Angina? If yes, was this in the last 12 months?	
No	41.94 ± 25.087
Yes	50.34 ± 23.218
p-value	0.140
Have you ever had/Do you have transient ischaemic attack (TIA)? If yes, was this in the last 12 months?	
No	42.34 ± 25.076
Yes	42.92 ± 24.714
p-value	0.943
Have you ever had/Do you have Diabetes? If yes, was this in the last 12 months?	
No	41.98 ± 25.084
Yes	45.15 ± 24.765
p-value	0.408
Have you ever been told by a doctor that you have high blood pressure?	
No	42.53 ± 25.099
Yes, but without medication	39.09 ± 24.428

(Continued)

TABLE 3 | Continued

Social and demographic data

Variable	Mean ± SD
Yes, with medication	42.12 ± 25.293
p-value	0.891
Have you ever been told by a doctor that you have high cholesterol?	
No	41.51 ± 25.118
Yes, but without medication	43.18 ± 27.818
Yes, with medication	49.04 ± 20.066
p-value	0.218
Have you ever been told by a doctor that you have abnormal heart rhythm (atrial fibrillation)?	
No	40.94 ± 25.060
Yes, but without medication	53.42 ± 20.744
Yes, with medication	57.42 ± 21.592
p-value	0.002
Where do you get most of your health information? Internet	
No	50.49 ± 28.028
Yes	38.41 ± 22.464
p-value	<0.001
Where do you get most of your health information? Newspaper/Magazine	
No	41.84 ± 25.201
Yes	45.80 ± 23.858
p-value	0.280
Where do you get most of your health information? Television	
No	43.57 ± 25.781
Yes	39.05 ± 22.672
p-value	0.086
Where do you get most of your health information? Health/fitness center	
No	41.89 ± 25.148
Yes	47.60 ± 23.474
p-value	0.206
Where do you get most of your health information? Friends	
No	44.21 ± 25.691
Yes	36.01 ± 21.609
p-value	0.002
Where do you get most of your health information? Church	
Yes	42.59 ± 24.971
No	16.12 ± 20.355
p-value	0.044
Where do you get most of your health information? Alternative practitioners	
No	42.49 ± 25.218
Yes	38.02 ± 19.068
p-value	0.419
Where do you get most of your health information?Nurse	
No	42.32 ± 25.357
Yes	42.61 ± 22.483
p-value	0.938

(Continued)

TABLE 3 | Continued

Social and demographic data

Variable	Mean ± SD
Where do you get most of your health information? Doctor	
No	45.83 ± 26.381
Yes	39.62 ± 23.628
p-value	0.014
Where do you get most of your health information? Family member	
No	44.79 ± 25.207
Yes	31.92 ± 21.494
p-value	<0.001
Where do you get most of your health information? Don't know	
No	41.37 ± 24.447
Yes	53.68 ± 29.142
p-value	0.025

dizziness" (25.1%) and "sudden severe headache with no known cause" (28%). On the other hand, call 112 was greatly chosen by the participants in situations where difficulty speaking presented together with sudden arm and face weakness. Moreover, 82.4% of the sample recognized the need to call 112 when the diagnosis of stroke was provided.

In the bivariate analysis, medical history of heart attack and atrial fibrillation were significantly associated with a higher mean STAT score ($p = 0.026$ and $p = 0.002$, respectively). On the other hand, getting health information from the internet was significantly linked to a lower mean STAT score ($p < 0.001$; **Table 3**).

In the multivariate analysis, the mean STAT scores of participants who get their information from the internet, a family member and church were statistically significantly lower (ß = −10.177, $p < 0.001$; ß = −9.069, $p = 0.001$; and ß = −36.975, $p = 0.001$, respectively). Also, no association was found between the SKT score and the STAT score (**Table 4**).

DISCUSSION

To date, there's a paucity of information regarding knowledge and response to stroke in the Lebanese community. Hence, it is important to assess the stroke awareness level in order to implement preventive measures especially regarding primary stroke prevention, targeting better outcomes, and diminishing morbidity and mortality.

Knowledge of Stroke
The current research showed that stroke-related knowledge in the Lebanese community is insufficient. Almost half of the respondents demonstrated a poor level of stroke knowledge which is similar to studies conducted in numerous other countries (26–29, 34, 35, 47–49).

Most of the participants (61%) were capable of identifying the pathological mechanism of stroke by answering that it is

due to blockage of the blood supply to the brain. This revealed that Lebanese adults had some awareness about the development of the illness. The understanding of the disease development is important for them to be able to distinguish a stroke from a heart attack which tend to be confused by a large number of people (50–53). This result is in accordance with studies conducted in Malaysia (66.7%) (48) and in Ireland (60.3%) (47), however the percentage is higher than studies conducted in India (31%) (54) and a previous study conducted in Lebanon where 44.6% of the participants stated the pathological mechanism of the disease (55). An explanation could be that in the current study, closed-ended questions were used instead of open-ended questions employed in the previously mentioned studies. Also, it is noteworthy to mention that the Arabic translation of stroke is more descriptive and therefore facilitates the understanding of disease development.

Moreover, there was a lack of knowledge about controllable risk factors of stroke which is a finding that is consistent with many previous studies (26–29, 34, 47, 56–64). This finding may provide an indication into the cause for the higher stroke prevalence in Lebanon compared to other developing countries in the middle East.

The well-recognized risk factors in our research were physical inactivity (70.5%), obesity (69.3%), hyperlipidemia (67.3%), and hypertension (52.9%). Similarly, numerous studies have revealed these 4 as being the most identified risk factors of stroke (22, 59, 65). In contrast, in a recent study conducted in Ethiopia among hypertensive patients, hypertension was the least recognized risk factor (3.6%) (28).

Interestingly, although smoking is a well-known stroke risk factor, it was the least perceived risk factor in our study (9.8%). This finding contrasts with many other studies (22, 59, 65) including a previous study conducted in Lebanon where smoking was one of the most recognized risk factors (55). Furthermore, participants underestimated the most pertinent risk factors of stroke-diabetes and atrial fibrillation-despite their high prevalence among respondents in our research. Only a small percentage recognized that they were important stroke risk factors (37.8 and 17.6%, respectively). Numerous research has also shown poor identification of diabetes and atrial fibrillation as risk factors for stroke (22, 57, 65, 66). On the other hand, participants with diabetes were associated with a higher level of stroke-related knowledge which is a result confirmed by several other studies (22, 67).

Living in Beirut was associated with a significantly higher level of stroke-related knowledge than living in Mount Lebanon. This result needs to be confirmed as the number of participants in Mount Lebanon was larger than that of Beirut (197 and 83, respectively).

In addition, research has demonstrated that educated and younger participants have a higher level of stroke-related knowledge (26, 54–59, 68, 69). Our results ad to the literature by confirming this association. It is noteworthy to mention that in Lebanon; the proportion of the population which is literate is higher among the younger adult population which could explain the latter.

Also, our findings revealed that non-smokers have a higher stroke knowledge level. This finding correlates with other studies conducted in Jordan and in Ireland (34, 47). This may be because non-smokers are more conscious about their health which stops them from smoking hence leading to a pursuit of health-related information.

Response to Stroke

Our results revealed a poor correlation between stroke symptoms and appropriate action. This may be due to insufficient knowledge to effectively recognize stroke symptoms and hence act accordingly, which is in accordance with a former study conducted in Lebanon (55). A similar result was reported in numerous other studies. The findings showed that knowledge of stroke symptoms was significantly associated with the intent to call 112 (24, 50, 70). Moreover, a study conducted in India showed a significant association between poor knowledge of warning signs and delay in hospital arrival (20).

Interestingly, our results showed that 82.4% participants would call 112 when provided with the diagnosis of stroke which is a finding reported in numerous other studies (66, 71–73). However, this result contrasts with Khalil and Lahoud's study where only 57.7% of the respondents would call 112 when stroke was suspected (54).

Moreover, in our study, only 36.8% of participants chose call 112 in response to specific warning signs. A comparable finding was reported in studies conducted in Australia and the US (24, 45).

In addition, our results revealed that the symptoms for which most participants would call 112 are difficulty speaking presented together with sudden arm and face weakness which is a consistent finding with other studies (45, 47). On the other hand, sudden dizziness was one of the symptoms with the lowest intent of respondents to call 112 which is in accordance to another study conducted in Ireland (47).

Furthermore, our findings showed that getting health information from the internet was negatively linked to adequate response to stroke. Tonsaker (74) highlighted that online health information-being difficult to regulate-can be misleading and hence patients might misinterpret it and make important health decisions that conflicts with appropriate medical practices.

It is important to note that there was no significant association between knowledge of stroke and the decision to call an ambulance in our study which is in agreement with a study conducted in Ireland (47). However, this differs from Lackland's et al. study which revealed a decline in stroke mortality in the US that was attributed to the implementation of interventions and programs resulting in better knowledge of stroke risk factors, hence improving stroke practice (38–42).

Also, our findings showed a positive relationship between having a medical history of atrial fibrillation and heart attack which is a finding that differs from a study conducted in Ireland where no association was found with the presence of any diagnosis of cardiovascular diseases (47) and another research in the US where a positive relationship was seen in participants with no prior history of heart attack (45).

TABLE 4 | Multivariate analysis taking the STAT score as the dependent variable.

Variable	Unstandardized Beta	Standardized Beta	p-value	Confidence Interval	
Model 1: linear regression taking the sociodemographic factors as independent variables					
Where do you get most of your health information? Internet	−10.177	−0.191	<0.001	−15.675	−4.679
Where do you get most of your health information? Family Member	−9.069	−0.155	0.001	−14.518	−3.619
Where do you get most of your health information? Church	−36.975	−0.153	0.001	−59.587	−14.364
Model 2: linear regression taking the SKT score as the independent variable					
SKT score	−0.004	−0.004	0.930	−0.104	0.095

Clinical Implications

Previous studies have shown that the achievement of primary preventive strategies and early treatment succeeding a stroke is strongly linked to the community's knowledge and practices of stroke (25, 35, 38–41, 56, 75). Sufficient stroke knowledge and perception could lead to rapid and accurate stroke identification, therefore timely management. Hence, public knowledge and the right practices regarding stroke are required, with aims to lessen the burden of stroke.

Our results revealed poor stroke-related knowledge and a poor relationship between stroke symptoms and intent to call 112. These results are disturbing bearing in mind the increasing occurrence of stroke in Lebanon. Therefore, these results warrant the need to develop and implement national community awareness campaigns. The latter can be designed through institutions, universities, medical care facilities such as doctor's clinics and pharmacies. The use of various media methods is also fundamental in order to disseminate the information and raise public knowledge. In addition, the development of health promotion agendas is of outmost importance in order to aid people embrace healthier lifestyles and subsequently reduce the risk of stroke. The provision of health education focusing on stroke risk factors, warning signs and appropriate action is crucial in order to reduce stroke incidence, morbidity and mortality.

Additionally, Lebanon's current economic and financial crisis is resulting in poor available infrastructure, facilities and qualified personnel despite ranking 23rd in the world for healthcare efficiency in 2019 (76). This adds to the importance of raising stroke awareness in the general public as the lack of amenities, services and equipment is alarmingly rising in Lebanon today.

Limitations and Strengths

Our study has faced numerous limitations. First, the sample in our study is not representative of all of the Lebanese people as our respondents filled a google form survey which would exclude nationals with no access or not familiar with technological advances leading to selection bias. Moreover, it is important to mention that the scales used in the current research are not validated in Lebanon yet. In addition, the questionnaire was designed with close-ended questions which can overestimate stroke knowledge of respondents. Furthermore, all of the respondents' characteristics and answers were self-reported, therefore the degree of true answers or confirming participant's statements is not possible in the current study which may have caused information bias. The current research is the first study aimed to assess stroke knowledge and practice in

adults 18 years and above residing in all five Lebanese districts. Previous research only targeted older adults living in Beirut (55). In addition, the weighting of the data according to age and gender allowed to adjust the sample representation in our study.

CONCLUSION

In conclusion, the survey findings revealed poor stroke-related knowledge in the Lebanese community. Knowledge of stroke risk factors was low, as was awareness of the need to call 112 in response to stroke symptoms. These elements result in delays in seeking medical care after stroke, with consequential repercussions for stroke outcome. Hence, it is essential to develop health education programs in order to raise public stroke awareness in Lebanon. Further studies are needed on a more representative sample of the Lebanese people, with the utilization of both close-ended and open-ended questions in order to confirm these findings.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Lebanese University Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS, PS, and HH contributed to conception and design of the study. SS organized the database, performed statistical analysis, and wrote the manuscript. SH and PS reviewed and approved the analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.891073/full#supplementary-material

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Bibliometrics and Visual Analysis of Adult-onset Still Disease (1976–2020)

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Background: Adult-onset Still Disease (AoSD) is a rare disorder without standardized diagnostic criteria. People are paying more and more attention to its research. At present, no published studies have assessed the AoSD field using bibliometric tools. This study aimed to analyze research hotspots and frontiers through bibliometrics to provide a scientific and accurate reference for new and existing researchers.

Methods: Data were obtained from the Web of Science core database and analyzed by CiteSpace, VOSviewer, and Microsoft Excel.

Results: Involving 86 countries and regions, a total of 11,121 authors published 2,199 articles in 676 journals. These studies were published from 1976 to 2020. The United States published the most related articles (397). The United States, France, Italy, and Germany were the top four countries with a high H-index. Authors and institutions with high number of published articles and high citations are mainly located in France and Italy. High-frequency keywords include classification, criteria, diagnosis, and therapy method. Keyword clustering covers the connection between AoSD and rheumatoid arthritis, disease diagnosis, classification, and risk factors.

Conclusions: The research on AoSD focuses on the diagnosis and differential diagnosis of the disease. Targeted therapy will become a research hotspot in the future, and relevant clinical research needs to appropriately expand the sample size and improve the credibility of the conclusions. The data reported in this study can serve as a useful resource for researchers studying AoSD.

Keywords: Adult-onset Still Disease (AoSD), bibliometrics, research trend, VOSviewer, Citespace

INTRODUCTION

Adult-onset Still Disease (AoSD) is a systemic autoinflammatory disease. In 1971, Bywaters analyzed the clinical and laboratory characteristics of 14 adult patients. He found that these characteristics were very similar to systemic-onset juvenile idiopathic arthritis (SoJIA), a condition also known as Still disease. From these observations, he named the disease AoSD (1).

The incidence of AoSD is low. Furthermore, at present, there is no unified understanding of the incidence and prevalence of the disease in different populations in the world. A French study showed that the incidence of AoSD is about 0.16 per 1,00,000 people (2). In Japan, the incidence of AoSD in men and women is 0.22–0.34 per 1,00,000 patients, respectively (3). Additionally, AoSD can occur in any age group and race; however, it is more prevalent in young (15–25 years) and middle-aged (36–46 years) people.

The main characteristics of AoSD include recurrent fever, joint pain or arthritis, skin lesions, hepatosplenomegaly, enlarged lymph nodes, abnormal liver function, increased peripheral blood leukocytes, a high neutrophil ratio, increased C-reactive protein, an enhanced erythrocyte sedimentation rate, and a high concentration of serum ferritin.

Multiple factors such as heredity, infection, and immune dysfunction may be related to the pathogenesis of AoSD; however, the exact mechanism or causes remain unknown. The human leukocyte antigen (HLA) genotype is closely related to the pathogenesis of several diseases. Furthermore, HLA-Bw35, HLA-B17, HLA-B18, HLA-B35, HLA-DR4, HLA-DRw6, etc., are thought to be closely related to the onset of several diseases (4–8). Additionally, interleukin-6 (IL-6), interleukin-8 (IL-8), serum amyloid A, and macrophage migration inhibitory factors are hypothesized to affect disease susceptibility (9–12). Given that similar symptoms of infection such as a sore throat appear before the onset of AoSD, we hypothesize that infectious factors are involved in the onset of the disease. In agreement with this hypothesis, the incidence of AoSD is related to a variety of viruses and pathogenic bacteria (13, 14).

Both the innate and adaptive arms of the host immune response are involved in the pathogenesis of AoSD, of which macrophages, neutrophils, and serum cytokines play a key role. Inflammasome activation, like NLRP3 inflammasome (NOD-, LRR-and pyrin domain-containing 3), by pathogen-associated molecular patterns and damage-associated molecular patterns (15, 16) increase interleukin-1β (IL-1β) and interleukin-18 (IL-18) levels by cysteine-containing aspartate proteolytic enzyme-1 (caspase-1) (17–19). This leads to the dysregulation of IL-6, IL-8, interleukin-17, and Tumor Necrosis Factor alpha (TNF-α) levels (20–22) and results in the induction of cytokine storm and, thus, contribute to AoSD pathogenesis.

FIGURE 1 | Process of study selection.
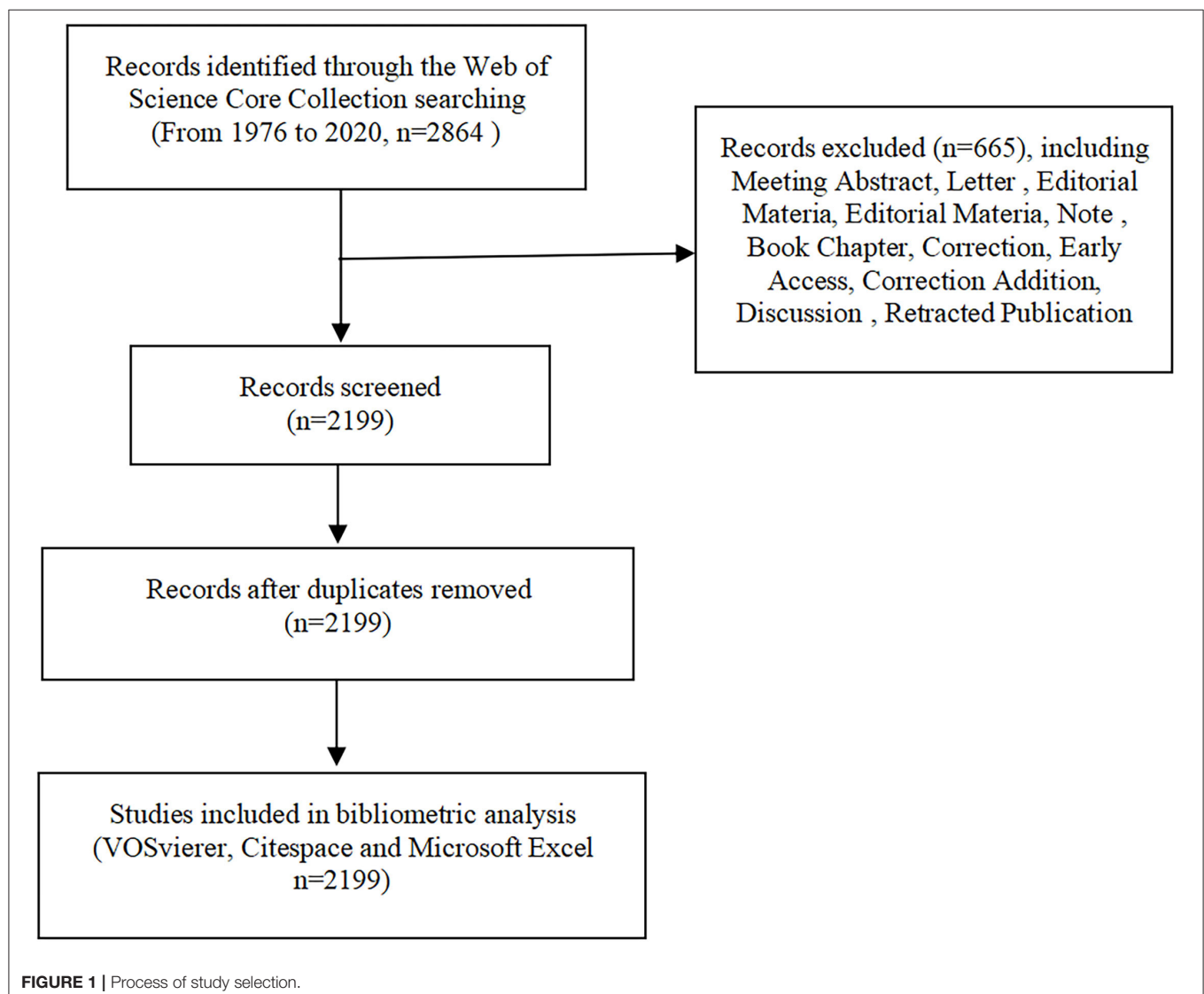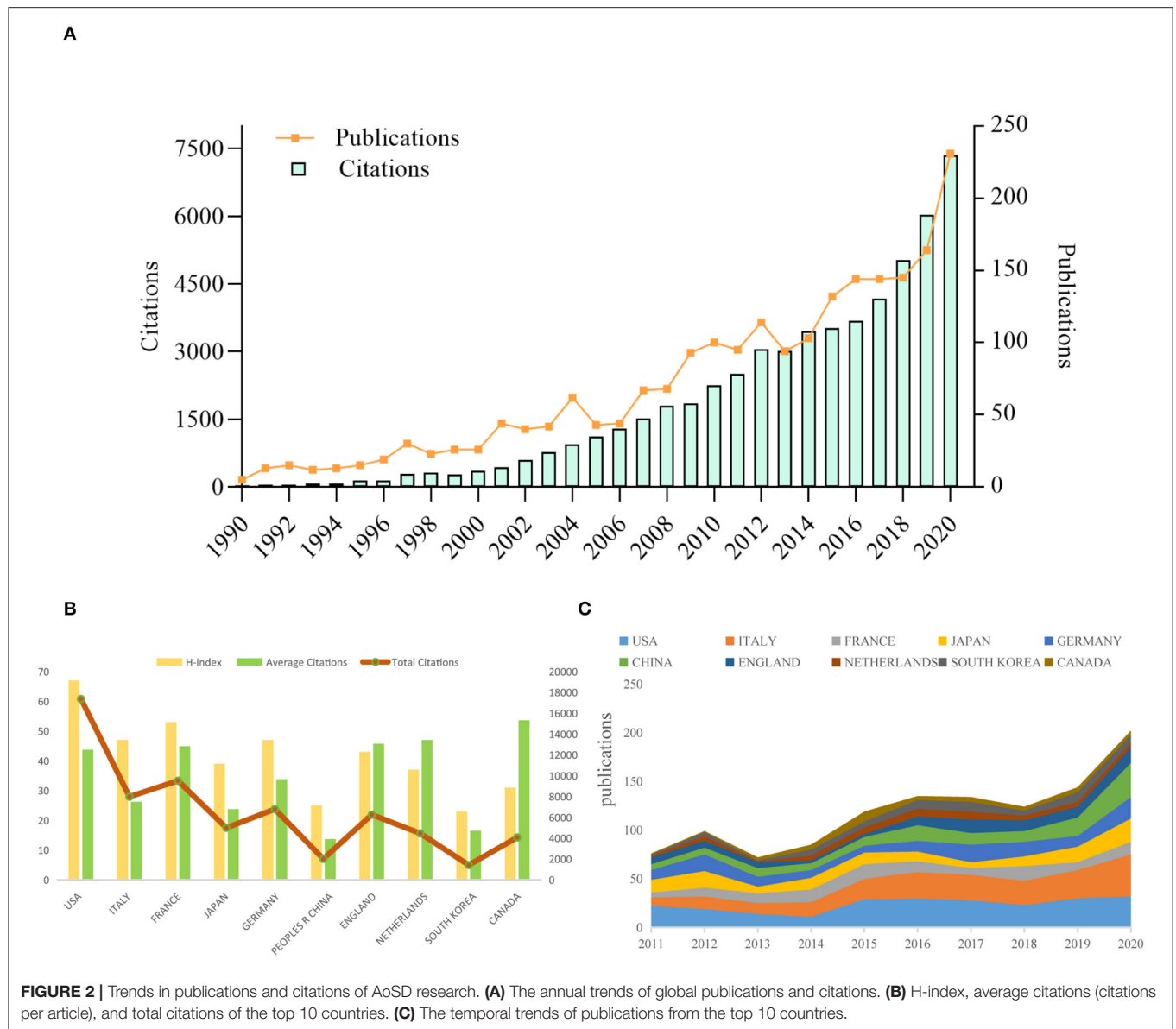
FIGURE 2 | Trends in publications and citations of AoSD research. **(A)** The annual trends of global publications and citations. **(B)** H-index, average citations (citations per article), and total citations of the top 10 countries. **(C)** The temporal trends of publications from the top 10 countries.

TABLE 1 | Top 10 countries by publications, citations, and centrality.

Rank	Country	Publications	% of 2,199	Total citations	Average citations	H-index
1	United States	397	18.054	17,372	43.76	67
2	Italy	304	13.824	7,986	26.27	47
3	France	212	9.641	9,519	44.9	53
4	Japan	210	9.55	4,995	23.79	39
5	Germany	201	9.141	6,794	33.8	47
6	China	147	6.685	2,016	13.71	25
7	England	137	6.23	6,265	45.73	43
8	Netherlands	95	4.32	4,463	46.98	37
9	South Korea	86	3.911	1,420	16.51	23
10	Canada	76	3.456	4,074	53.61	31

Bibliometrics is a comprehensive knowledge system that integrates mathematics, statistics, and linguistics. It is widely used to explore development trends and research frontiers in various fields (23). However, there is no bibliometric study for AoSD. Therefore, we conducted a bibliometric study to evaluate all available evidence for AoSD. Here, we aim to provide an up-to-date overview of the status of AoSD with the help of a variety of bibliometric tools.

MATERIALS AND METHODS

Eligibility Criteria

This study was included literatures on AoSD as the research topic. Article types were limited to "article" and "review." Conference abstracts, letters, expert views, editorial materials, corrections, retractions, and proceedings paper were excluded.

Search Strategy and Screening

All publications included in this study were collected from the Science Citation Index Expanded (SCI-E) through the Web of Science Core Collection (WoSCC) database on October 24, 2021. The search formula was set to TS = (Adult-onset Still Disease), and the period of published studies assessed was from 1976 to 2020, the language restriction was English. Two researchers (BH Bao and BW Xu) cross-checked the included article, and when there were disparities, the third researcher (XY Meng) made a final decision. The process of study screening is shown in **Figure 1**.

Data Analysis Methods

VOSviewer version 1.6.17, Citespace 5.8.R3 and Microsoft Excel 2020 are used for data analysis and visualization of AoSD article studies. VOSviewer and Citespace are bibliometric analysis softwares. These softwares were used for co-word analysis, co-citation analysis, and article coupling analysis. They can visualize the research results and has unique advantages in clustering technology and map display (24). Microsoft Excel was used to draw relevant tables and illustrate the annual trend of publications and references.

RESULTS

Temporal Trends of Publications and Citations

By using search strategy, a total of 2,864 published studies and reviews were retrieved. After the removal of duplicate documents, 2,199 articles remained. Changes in the number of publications and citations can reflect the development status of a field and predict future research trends. The total citations and average citations were 63,073 and 28.68, respectively. The H-index was 106. Searching within the WoSCC database, the first available article on AoSD was published in American Family Physician in 1976. In the past 10 years, the number of publications and citations of AoSD article has steadily increased year over year. In 2020, the number of publications and citations of related articles reached peaked at 231 and 11,731. As shown in **Figure 2A**.

TABLE 2 | Top 10 institutions distributed by publications and centrality.

Rank	Institution	Publications	Original country
1	Assistance Publique Hopitaux Paris	105	France
2	Institut National De La Sante Et De La Recherche Medicale	68	France
3	Sorbonne Universite	53	France
4	Universite de Paris	53	France
5	University of London	48	England
6	Harvard University	43	United States
7	Hopital Universitaire Pitie Salpetriere	40	France
8	Sapienza University Rome	38	Italy
9	University of Padua	35	Italy
10	Charite Medical University of Berlin	33	Germany

Country/Region and Institution Characteristics

From 1976 to 2020, scholars from 86 countries and regions have published AoSD research. Among them, scientists from the United States published the most (397, 18.054%). The Top 10 countries with more than 200 publications included Italy (304, 13.824%), France (212, 9.641%), Japan (210, 9.55%), and Germany (201, 9.141%) (**Table 1**). From the number of publications in the past 10 years, it can be observed that the number of AoSD publications from the Top 10 countries has been steadily increasing (**Figure 2C**). Furthermore, from the average number of citations within the same period, Canada (53.61), Netherlands (46.98), and England (45.73) are ranked in the Top three and the United States (67), France (47), Italy, Germany (47) were the Top four countries with the highest H-index (**Figure 2B** and **Table 1**). Together, these data indicate that the United States, Canada, Brazil, Italy, and other countries have made a substantial contribution to AoSD research.

Regarding specific research institutions, we found that 2,588 research institutions have conducted AoSD research. The main institutions by number of publications include Assistance Publique Hopitaux Paris (105 publications), Institut National De La Sante Et De La Recherche Medicale (68 publications) and Sorbonne Universite (53 publications). These data indicate that these three institutions are specialized in the field of AoSD research. Further, it is evident that France occupies a dominant position in the field (**Table 2**).

Academic Collaboration

Academic exchanges and cooperation between different countries/regions, institutions, and authors play an important role in expanding the depth and horizons of research. When parameters of academic cooperation and exchange in AoSD research were assessed, it is evident that collaboration, training, and information exchange occur at multiple levels (**Figure 3**).
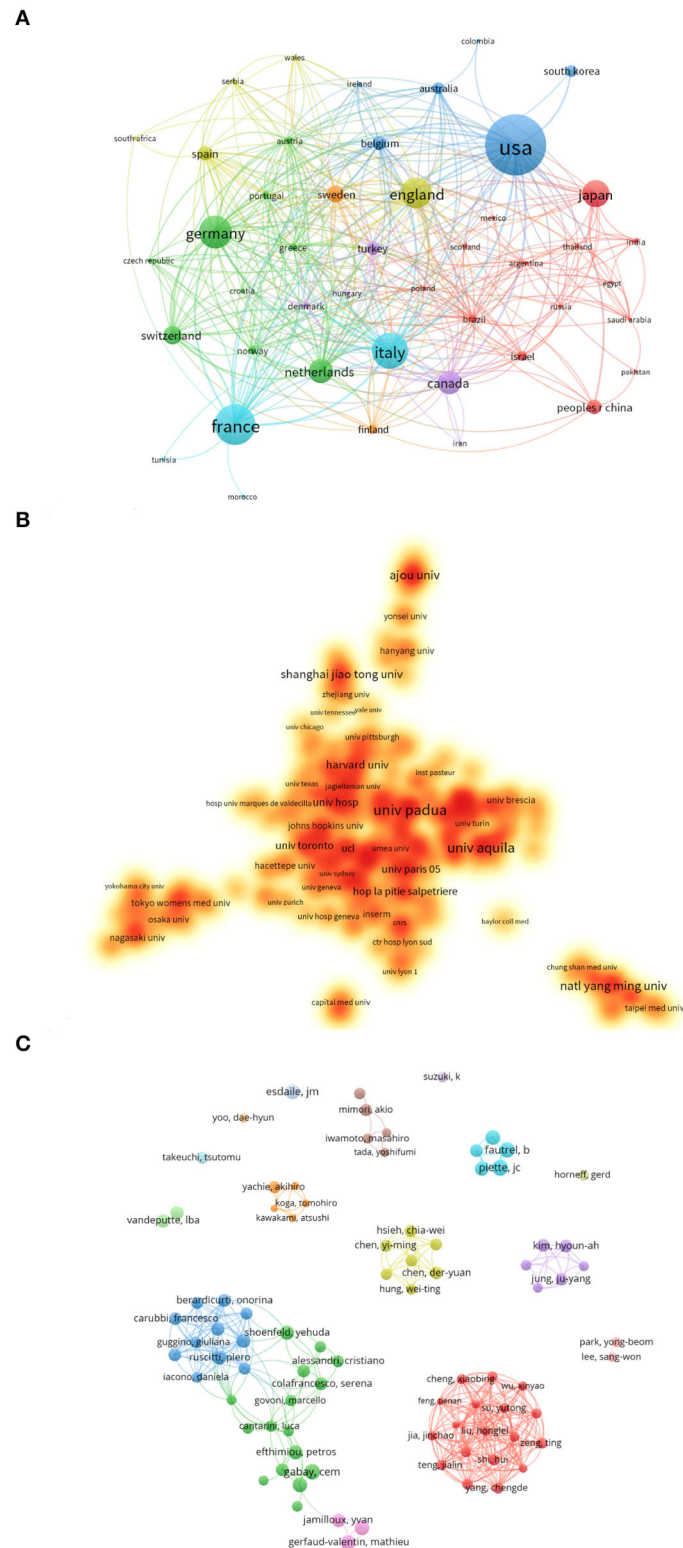
FIGURE 3 | Academic collaboration between different countries/regions, institutions, and authors in AoSD research area. **(A)** Academic collaboration between different countries/regions. **(B)** Collaboration between different institutions. **(C)** Collaboration between different authors.

TABLE 3 | Top 10 authors distributed by publications and citations.

Rank	Author	Publications	Country	Institution	Rank	Cited author	Total citations	Average citations	H-index	Country	Institution
1	Giacomelli R	27	Italy	University of Aquila	1	Fautrel B	1,663	87.53	16	France	Assistance Publique Hopitaux Paris (APHP)
2	Ruscitti P	26	Italy	University of Aquila	2	Piette JC	901	103.7	10	France	Assistance Publique Hopitaux Paris (APHP)
3	Kim Ha	25	South Korea	Ajou University	3	Giacomelli R	753	27.89	16	Italy	University of Aquila
4	Suh CH	24	South Korea	Ajou University	4	Gabay C	740	148	5	Switzerland	University of Geneva
5	Chen DY	21	China	China Medical University	5	Esdaile JM	623	124.8	5	Canada	McGill University
6	Cipriani P	20	Italy	University of Aquila	6	Bourgeois P	616	115.5	6	France	Assistance Publique Hopitaux Paris (APHP)
7	Fautrel B	19	France	Assistance Publique Hopitaux Paris (APHP)	7	Shoenfeld Y	612	61.2	9	Israel	Tel Aviv University Sackler Faculty of Medicine
8	Jung JY	19	South Korea	Ajou University	8	Gerfaud-Valentin M	607	67.44	8	France	University of Claude Bernard Lyon 1
9	Yang CD	17	China	Shanghai Jiao Tong University	9	Seve P	572	67.44	8	France	University of Claude Bernard Lyon 1
10	Giacomelli R	27	Italy	University of L'Aquila	10	Fautrel B	1,663	87.53	16	France	Assistance Publique Hopitaux Paris (APHP)

VOSviewer software was used to visualize the collaboration between countries, institutions, and authors (**Figure 3A**). Each node represents a different country/region. The connection between the nodes represents the cooperative relationship, and the node size represents the number of published studies that have arisen from their collaboration. Of the total published articles, 48 countries/regions published at least five research articles. The United States, Italy, Germany, and France have collaborated the most in AoSD research, which is highly consistent with the observation made for the Top 10 countries in **Table 1**.

The node connection length reflects the closeness of cooperation between two different institutions. Our analysis revealed that a total of 216 research institutions have published at least five research documents. Circles/nodes in different colors represent a cooperative group. Twelve cooperative groups with the closest cooperation were identified. The University of Padua, the University of L'Aquila, and Harvard University have carried out the most academic cooperation with other research institutions. As shown in **Figure 3B**.

Co-author analysis revealed a total of 11,121 co-authors in the AoSD field. Giacomelli R (27 articles) has published the most articles, followed by Ruscitti P (26 articles) and Kim Ha (25 articles) (**Table 3**). Our data indicate that 85 authors have published more than five articles. After clustering these scientists, 16 main cooperative groups were formed (**Figure 3C**). Among the two largest cooperative groups, Ciccia Francesco and Liu Honglei occupy key positions in the cooperative network, indicating that their research in this field has been significantly cooperative.

Distribution of Co-cited Authors

The Top three most-cited authors were Fautrel B (1,663 citations), followed by Piette JC (901 citations), and Giacomelli R (753 citations). The majority of institutions where the Top 10 authors, by publications and citations, were affiliated were located in France and Italy (**Table 3**). Yamaguchi M has the highest number of co-citations, followed by Fautrel B, and Pouchot J (**Figure 4**). These authors have been co-cited more than 380 times, indicating that their AoSD research has received widespread attention.

Distribution of Journals

The studies and reviews assessed here were published in 676 journals, of which 23 journals published more than 20 articles related to AoSD. The impact factor (IF) and journal quartile were obtained from Journal Citation Reports 2020. The Top four most productive journals are *Clinical Rheumatology* (IF 2.98), *the Journal of Rheumatology* (IF 4.666), *Rheumatology International* (IF 2.631), and *Medicine* (IF 1.889). The Top four journals cited are *the Journal of Rheumatology* (IF 4.666), *Medicine* (IF1.889), *the Annals of the Rheumatic Diseases* (IF 19.103), and *Clinical Rheumatology* (IF 2.98); all of which have been cited more than 1,500 times (**Table 4**). The Top three most cited journals are *the Journal of Rheumatology* (IF 4.666), *the Annals of the Rheumatic Diseases* (IF 19.103), and *Arthritis & Rheumatology* (IF 10.995) (**Figures 5A,B**). The majority of the published articles, including

FIGURE 4 | VOSviewer visualization map of co-cited authors devoted to AoSD research.
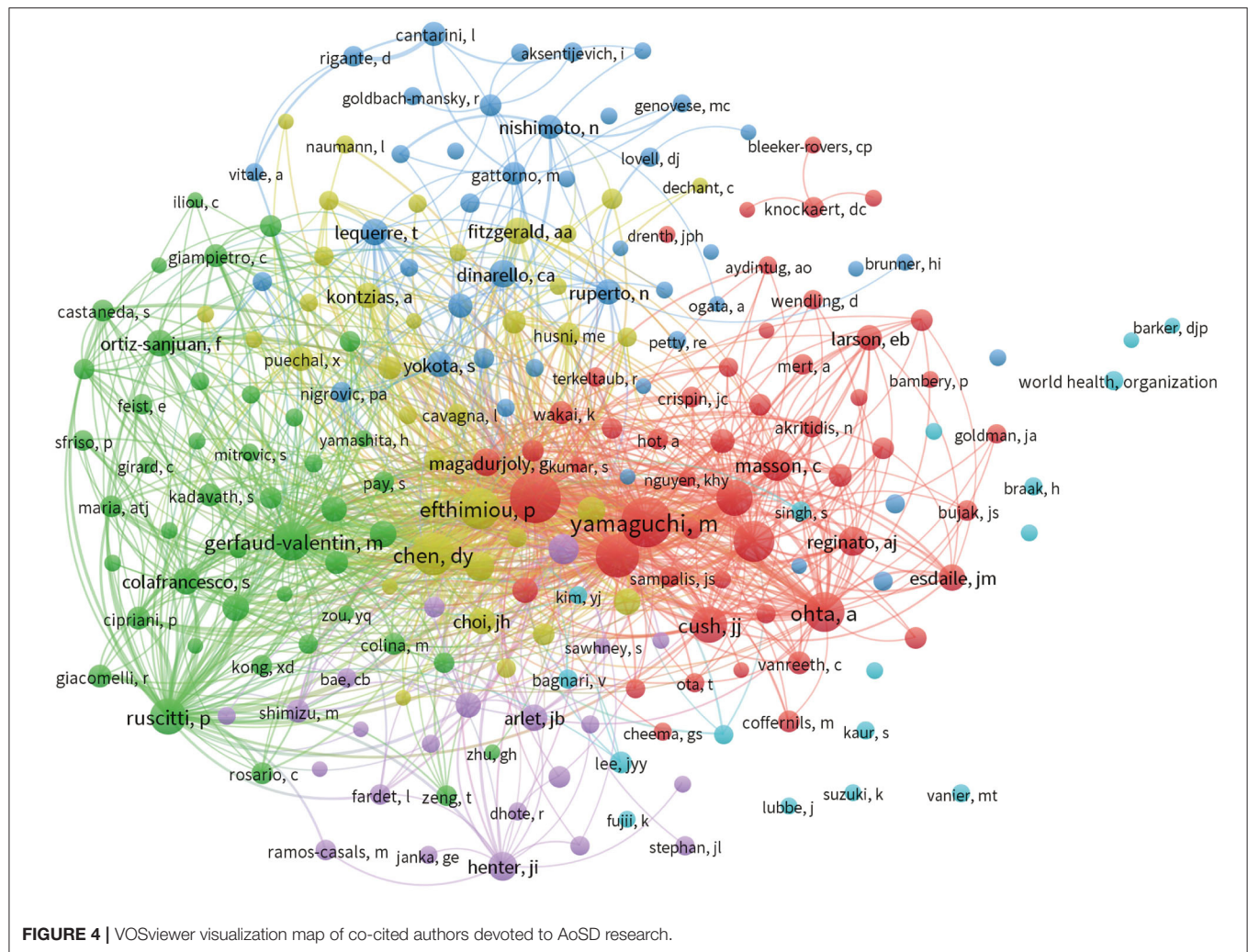
the Top 10 most cited journals, are distributed in Q1 or Q2 (**Table 4**). These data indicate that these journals have a relatively important influence on AoSD research.

Analysis of Highly Cited Articles and Co-cited References

The Top thee co-cited references as follows: "Preliminary criteria for classification of adult stills disease" by Yamaguchi et al. (25) (653 citations). This article attempted to design classification criteria for AoSD. In that paper, AoSD criteria were proposed to be fever, arthralgia, typical rash, and leukocytosis as major, and sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, and the absence of rheumatoid factor and antinuclear antibody as minor criteria. A positive diagnosis was defined as a patient presenting with five or more criteria including two or more primary criteria (25). The second was "Still's disease in the adult." by Bywaters (1) (354 citations). In this study, Bywaters first identified an inflammatory disease in young people and observed that the disease was similar to the childhood-onset Still's disease (that is SoJIA). Whilst the exact pathogenesis of the disease remains unclear, there

is published homology between AoSD and SoJIA. Third was "Adult stills disease-manifestations, disease course, and outcome in 62 patients" by Pouchot et al. (8) (323 citations). In that study, Pouchot made a preliminary assessment of the clinical and laboratory manifestations, course of disease, outcome, and HLA association of 62 adult patients with Styr's disease from five universities in Canada. He concluded that that the close monitoring of liver function test in patients with AoSD, was important to improve patient outcomes, especially in the early course of the disease and regardless of whether patients use aspirin or other non-steroidal anti-inflammatory drugs (8).

Co-cited references clustering can reflect the frontier direction of research field or unresolved scientific topics to a certain extent, which contains the emerging trend of research. The main clusters of co-cited references on AoSD focus on the treatment (#2, #5), clinical manifestations and accompanying symptoms (#1, #3, #8, #9, #16), differentiation from other rheumatic immune diseases (#4, #6), and autoimmune reactions (#7). As shown in **Table 5** and **Figure 6**.

The Top three articles with the most citations included Yamaguchi et al. (26) (1,081 citations), Pouchot et al. (8) (482

TABLE 4 | Top 10 journals distributed by publications and citations.

Rank	Journal	Publications	% of 2,219	IF (JCR2020)	JIF quartile	Journal	Total citations	Average citations	H-index	IF (JCR2020)	JIF quartile
1	Clinical Rheumatology	79	3.593	2.98	Q3	Journal of Rheumatology	3,467	65.45	29	4.666	Q2
2	Journal of Rheumatology	53	2.41	4.666	Q2	Medicine	1,946	47.54	18	1.889	Q2
3	Rheumatology International	46	2.092	2.631	Q3	Annals of the Rheumatic Diseases	1,836	63.31	20	19.103	Q1
4	Medicine	41	1.864	1.889	Q2	Arthritis & Rheumatology	1,731	25.84	17	10.995	Q1
5	Clinical and Experimental Rheumatology	39	1.774	4.473	Q2	Clinical Rheumatology	1,569	19.87	22	2.98	Q3
6	Annals of the Rheumatic Diseases	29	1.319	19.103	Q1	Journal of Clinical Endocrinology & Metabolism	1,035	43.08	30	5.958	Q1
7	Modern Rheumatology	29	1.319	3.023	Q3	Rheumatology	986	46.95	16	7.580	Q1
8	Revue De Medecine Interne	24	1.091	0.728	Q4	Seminars in Arthritis and Rheumatism	941	42.77	14	5.532	Q2
9	Internal Medicine	23	1.046	2.048	Q2	Journal of Allergy and Clinical Immunology	895	127.86	7	10.793	Q1
10	Seminars in Arthritis and Rheumatism	22	1	5.532	Q2	Autoimmunity Reviews	878	73.25	11	9.754	Q1

citations) and Gabay et al. (27) (435 citations). The article entitled "IL-1 pathways in inflammation and human diseases" by Gabay et al. (27) has been cited 435 times. This review systematically described published research relating to the IL-1 pathway and inflammation development and treatment. The review found that the human IL-1 receptor antagonist, Anakinra, produced by gene recombination technology affected AoSD (27). As shown in **Tables 6**, 7.

Analysis of Keywords

Keywords can also reflect frontiers and hotspots in a particular field. The Top 10 keywords with the highest occurrence frequencies in the article assessed in this study were "classification" (184), "criteria" (177), "rheumatoid-arthritis" (161), "juvenile idiopathic arthritis" (144), "manifestations" (139), "diagnosis" (137), "children" (129), "macrophage activation syndrome" (98), "adults" (94), and "efficiency" (83).

By clustering keywords with a frequency >5, a total of 446 eligible keywords were clustered into seven groups. Nodes with the same color represent the same cluster (**Figure 7A**). The clustering theme covers the links with rheumatoid ailment, disease diagnosis, classification, risk factors, and other aspects (**Figure 7B**). And keywords with a frequency of occurrence higher than 20 were screened for cluster presentation, as shown in **Table 8**. This is similar to the results of keywords burst. Keyword burst results show that the clinical prognosis judgment of AoSD, disease classification and the biological agents treatment (such as Anakinra) will be the research hotspots in the future (**Figure 8**).

DISCUSSION

This study uses a variety of bibliometric software and tools to analyze the published research article on AoSD based on the WoSCC database. Studies have shown that the earliest retrospective article was published in 1976 (28).

By 2020, the annual number of publications and citations of AoSD-related research showed an overall upward trend, thus highlighting the rapid development of AoSD studies and sustained interest in its research. However, as an orphan disease, AoSD has a low incidence in the population with the prevalence rate estimated to be one case per million people in Europe and 10 cases per million people in Japan (2, 3). This low incidence has translated into fewer published studies relative to other rheumatic diseases. From 1976 to 2020, a total of AoSD 2,199 articles were published indicating the growing importance of AoSD research in spite of its low incidence. In addition, compared with other rare immune-related diseases such as Primary Combined Immune Deficiency (26), Chediak-Higashi Syndrome (29), and Chronic Primary Granulomatous Disease (30), which publications were 866, 1,252, and 1,425, respectively. The result indicates that AoSD may attract more interest than these rare diseases in terms of publications. However, compared with common rheumatic immune diseases such as rheumatoid arthritis (more than 190,000 articles) and systemic lupus erythematosus (more than
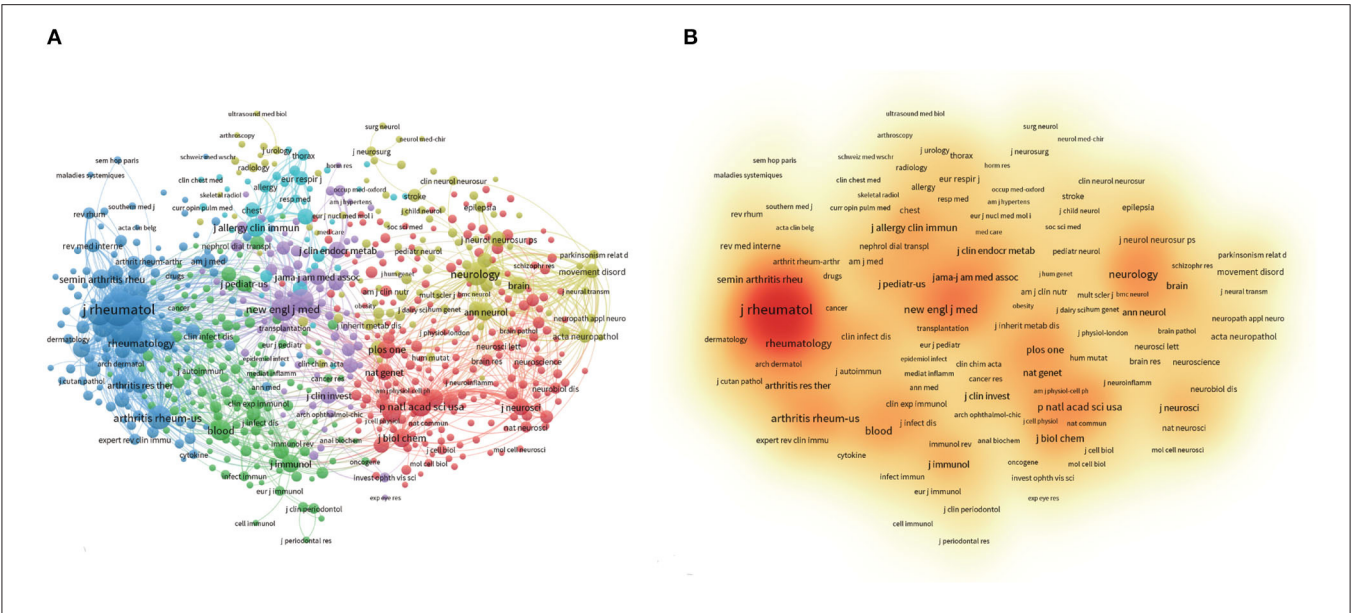
FIGURE 5 | VOSviewer visualization map of most commonly cited journals related to AoSD research. **(A)** Co-citation network of journals. **(B)** The density map of the most commonly cited journals.

80,000 articles), the publication count of papers on AoSD is still significantly insufficient.

Through the comprehensive and systematic summary of the research topics, trends, and global research on the impact of AoSD, scholars can quickly and preliminarily understand the current state of AoSD research. The H-index reflects the academic achievements of countries, institutions, or individuals in a certain field. The higher the H-index, the greater the academic influence. From the perspective of regional distribution, the United States is the global leader in terms of both the number of published article and H-index in AoSD-related research. Specifically, AoSD research originating in the United States has significantly contributed to the field. However, in the current study, further analysis of research institutions and individuals revealed that France and Italy may have superior contributing roles to global AoSD research. This is especially valid when assessing the Top 10 authors by the number of publications and citations. Further, these data indicated that no American scholars were found in the Top 10, and French and Italian scholars occupy the majority.

Keyword cluster analysis can highlight current research hotspots. In agreement with the research direction of highly cited articles and co-cited references, our data indicate that the research hotspots of AoSD are mainly related to the identification and diagnosis of the disease. These hotspots may be attributed to the fact that as an orphan disease, the pathogenesis of AoSD is not clear, and multiple factors including heredity, infection, and immune dysfunction may contribute to AoSD development. As an immune-related disease, AoSD is difficult to distinguish from juvenile rheumatoid arthritis and rheumatoid arthritis (RA) in the initial clinical diagnosis.

TABLE 5 | Major clusters of co-cited references.

Cluster ID	Cluster label	Size	S-value	Mean (year)
#1	Myocarditis	103	0.885	2016
#2	Infliximab	97	0.868	2008
#3	Haemophagocytic lymphohistiocytosis	95	0.955	2001
#4	Stills disease	80	0.955	2016
#5	Tocilizumab	60	0.99	1988
#6	Adult stills disease	59	0.933	2010
#7	NLRP3	59	0.964	1994
#8	Paraneoplastic syndrome	59	0.945	2006
#9	Pulmonary arterial hypertension	37	0.94	2013
#16	Atypical cutaneous manifestations	31	0.94	2014
#19	Juvenile idiopathic	15	1	2014

Additionally, multiple difficulties exist in the diagnosis of AoSD resulting in a lack of a unifying clinical diagnostic gold standard. Traditionally, the diagnostic criteria for AoSD have mainly been based on four main symptoms including fever, arthritis or joint pain, rash, and increased white blood cell and neutrophil counts (14). Fautrel proposed a new diagnostic classification criterion in 2002. His set of eight diagnostic classification criteria included spiking fever $\geq 39°C$, arthralgia, maculopapular rash, transient erythema, pharyngitis, leukocyte count $\geq 10,000/mm^3$, polymorphonuclear count $\geq 80\%$, and glycosylated ferritin $\leq 20\%$. Of these criteria, maculopapular rash and leukocyte count $\geq 10,000/mm^3$ are considered to be secondary, and the remaining six signs are considered to be the primary criteria. Using these parameters, a positive AoSD diagnosis would be defined as a patient presenting with four primary criteria, or three primary criteria +2 secondary

FIGURE 6 | Citespace visualization map of major clusters of co-cited references.
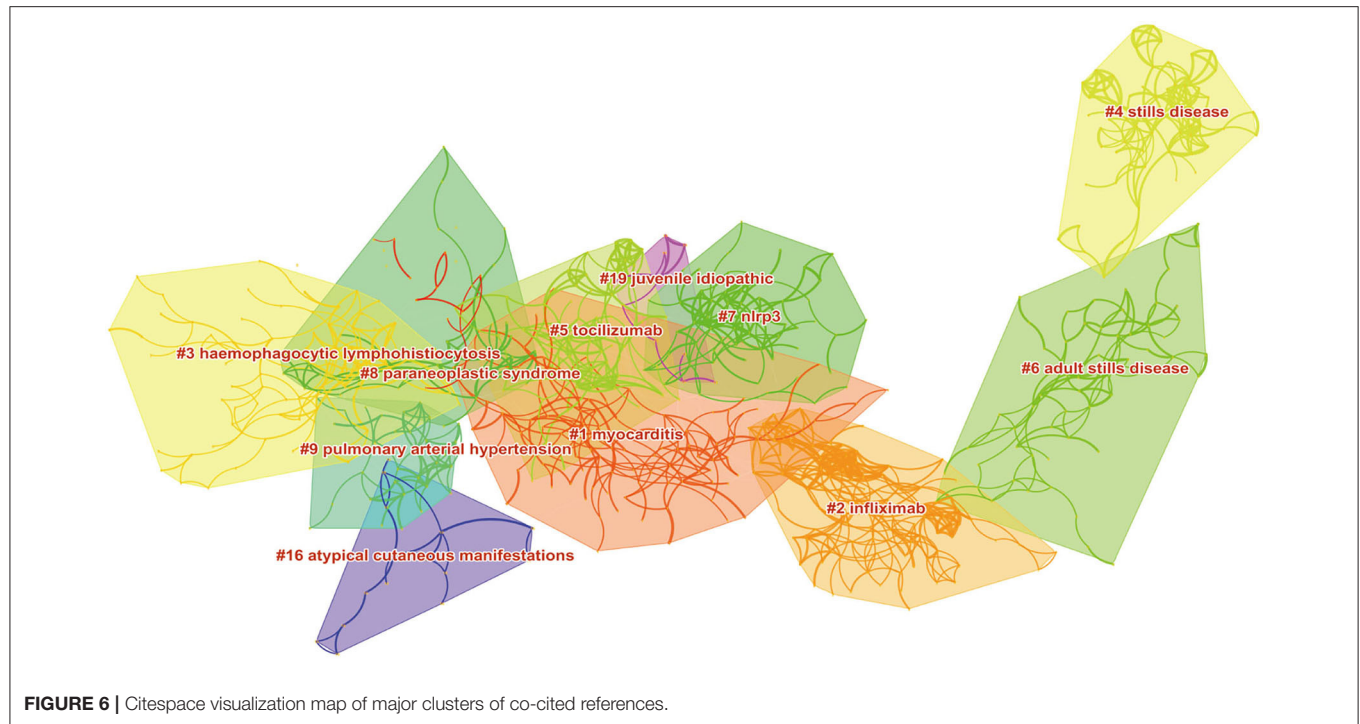
TABLE 6 | Top 10 co-cited reference.

Rank	Author	Title	Source	Citations
1	Yamaguchi, M	Preliminary criteria for classification of adult stills disease	*Journal of Rheumatology*	653
2	Bywaters EG	Still's disease in the adult	*Annals of the Rheumatic Diseases*	354
3	Pouchot, J	Adult stills disease—manifestations, disease course, and outcome in 62 patients	*Medicine*	323
4	Cush, JJ	Adult-onset stills disease—clinical course and outcome	*Arthritis and Rheumatism*	197
5	Efthimiou P	Diagnosis and management of adult onset Still's disease	*Annals of the Rheumatic Diseases*	175
6	Fautrel, B	Proposal for a new set of classification criteria for adult-onset Still disease	*Medicine*	168
7	Gerfaud-Valentin, M	Adult-onset Still's disease	*Autoimmunity Reviews*	150
8	Chen DY	Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease	*Journal of Rheumatology*	132
9	Fautrel, B	Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France	*Annals of the Rheumatic Diseases*	128
10	Reginato AJ	Adult onset Stills disease—Experience In 23 patients and literature-review with emphasis on organ failure	*Seminars in Arthritis and Rheumatism*	128

TABLE 7 | Top 10 cited articles.

Rank	Author	Title	Source	Citations
1	Yamaguchi, M	Preliminary criteria for classification of adult stills disease	*Journal of Rheumatology*	1,081
2	Pouchot, J	Adult stills disease—manifestations, disease course, and outcome in 62 patients	*Medicine*	482
3	Gabay, C	IL-1 pathways in inflammation and human diseases	*Nature Reviews Rheumatology*	435
4	Lequerre, T	Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France	*Annals of the Rheumatic Diseases*	286
5	Cush, JJ	Adult-onset stills disease—clinical course and outcome	*Arthritis and Rheumatism*	263
6	Gerfaud-Valentin	Adult-onset Still's disease	*Autoimmunity Reviews*	255
7	Fitzgerald, AA	Rapid responses to anakinra in patients with refractory adult-onset Still's disease	*Arthritis and Rheumatism*	251
8	Fautrel, B	Proposal for a new set of classification criteria for adult-onset Still disease	*Annals of the Rheumatic Diseases*	243
9	Efthimiou P	Diagnosis and management of adult onset Still's disease	*Annals of the Rheumatic Diseases*	241
10	Rosario, C	The Hyperferritinemic Syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome	*BMC Medicine*	235

FIGURE 7 | Analysis of all keywords in studies related to AoSD research. **(A)** VOSviewer visualization map of co-occurring keywords. **(B)** The density map of keywords. (The closer the keyword node color is to red, the higher the frequency of its co-occurrence).

FIGURE 8 | Top16 keywords with the strongest citation bursts.

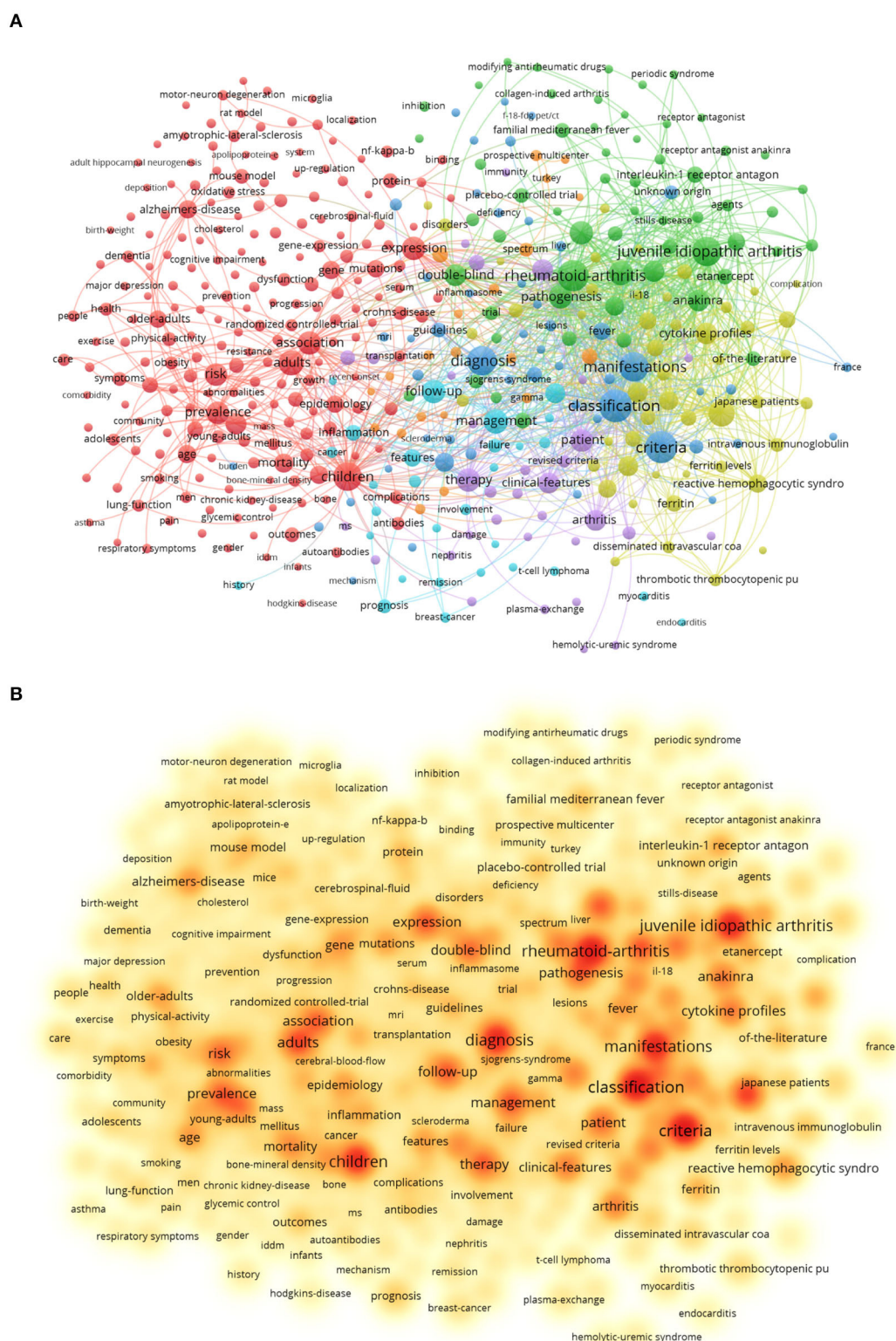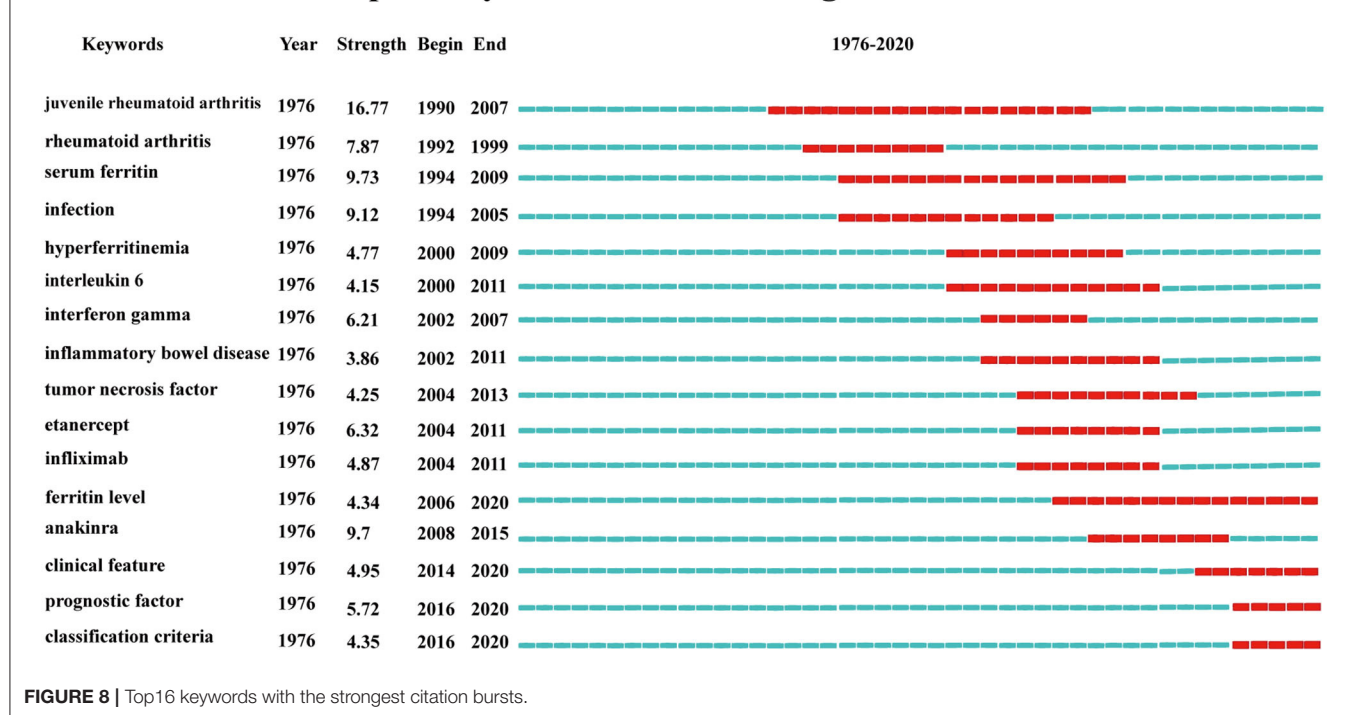criteria. Studies have shown that these diagnostic criteria have a higher sensitivity relative to traditional diagnostic strategies (31). Because the symptoms of AoSD are diverse and systemic, it is necessary to differentiate AoSD from a variety of other diseases such as infections, malignancies, and other chronic rheumatism during diagnosis. These newly proposed criteria may assist with this. There are still a variety of diagnostic and classification criteria (32), but most of the criteria are exclusionary diagnosis. Even after the diagnosis is made, the changes of the disease should be observed at any time during treatment and follow-up. Since the research on AoSD is relatively short and many contents are not yet perfect, developing a diagnostic standard with higher specificity is still a hotspot and difficulty in future research.

Previously, non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs have been used for the treatment of AoSD; however, their curative effect is poor. Further, in ∼40% of cases, patient symptoms remain unaffected by traditional treatment (33, 34). Common anti-rheumatic immune drugs such as interferon-γ, etanercept and anakinra are also widely used clinically (35). The activation of innate immunity and the dysregulation of cytokines are important mechanisms contributing to the pathogenesis of AoSD. IL-1β, IL-18, IL-6, and TNF-α are elevated in the serum, skin lesions, and synovial membrane of AoSD patients. The targeted therapy for these factors has been successfully applied in other models of chronic rheumatic disease and may provide a reference for the treatment of AoSD. Many studies have shown that biological agents have good safety and effectiveness in the treatment of refractory AoSD,

but the sample size of clinical trials is obviously inadequate (20, 36, 37).

We found that research on targeted therapy for AoSD has been on the rise. As early as 2007, Efthimiou suggested that recent advances in basic immunology have improved our ability to hinder the pathogenic mechanisms associated with AoSD, and discussed the impact of targeted anti-inflammatory cytokine-based targeted therapies on AoSD (14, 38, 39). An increasing number of clinical trials have demonstrated that targeting these proinflammatory cytokines may be effective in controlling AoSD (40). Antagonists of IL-1β and its receptor have been successfully used to treat AoSD (41). Three anti-IL-1β biologics, namely, anakinra, canakinumab, and rilonacept, which are used to control AoSD, are currently available on the market. In the results of this study, Anakinra is one of the current research hotspots, and the publications of papers mentioning AoSD with Anakinra as 227 on WOS data. To our knowledge, a randomized, double-blind, placebo-controlled, multicenter, phase III study to assess the efficacy and safety of anakinra in the treatment of AoSD (https://clinicaltrials.gov/ct2/show/study/NCT03265132), just concluded the update in June 2021, and no relevant literature has been published. In addition, systematic reviews are indicating that the use of IL-1β inhibitors in AoSD has led us to a new era of targeted therapy for AoSD (42). Whilst TNF-α inhibitors, as the first biological agent for the treatment of AoSD, have a good curative effect in chronic inflammatory joint diseases (especially RA), the curative effect in the treatment of AoSD is poor (43). Therefore, we believe that as molecular biology progresses, targeted therapy will play a more beneficial role in AoSD.

TABLE 8 | Major clusters of keywords.

Cluster	Keyword	Number	Cluster	Keyword	Number
1	Children	129	3	Arthritis	57
1	Disease	124	3	Interleukin-18	49
1	Adults	94	3	Cytokine	39
1	Expression	78	3	Clinical-manifestations	34
1	Prevalence	73	3	pathological tissues	32
1	Risk	70	3	Ferritin	31
1	Risk-factors	66	3	Inflammation	30
1	Mortality	48	3	Marker	30
1	Alzheimer's-disease	43	3	Peripheral-blood	28
1	Age	42	3	Classification criteria	27
1	Gene	41	3	Interferon-gamma	25
1	Epidemiology	38	3	Classification	184
1	Mutations	37	4	Criteria	177
1	Older-adults	36	4	Manifestations	139
1	Proteins	32	4	Experience	54
1	Population	30	4	Features	38
1	Cardiovascular-disease	28	4	Adult-onset	23
1	Natural-history	26	4	Prognosis	21
1	Quality-of-life	25	4	Diagnosis	137
1	Mouse model	24	5	Management	82
1	Women	23	5	Infection	48
1	Physical-activity	21	5	Fever	39
1	Symptoms	21	5	Guidelines	26
2	Rheumatoid-arthritis	161	5	Placebo-controlled trial	23
2	Juvenile idiopathic arthritis	144	5	Therapy	77
2	Efficacy	83	6	Double-blind	67
2	Follow-up	78	6	Systemic-lupus-erythematosus	57
2	Onset stills-disease	76	6	Interleukin-6	24
2	Pathogenesis	75	6	Trial	22
2	Anakinra	62	6	Inflammatory-bowel-disease	21
2	Clinical-features	59	6	Macrophage activation syndrome	98
2	Multicenter	49	7	Tumor-necrosis-factor	61
2	Tocilizumab	35	7	Serum ferritin	55
2	Interleukin-1 receptor antagonist	33	7	Juvenile rheumatoid-arthritis	53
2	Etanercept	30	7	Reactive hemophagocytic syndrome	41
2	Safety	28	7	Hemophagocytic syndrome	40
2	Methotrexate	26	7	Lymphohistiocytosis	26
2	Familial mediterranean fever	24	7	Prognostic-factors	25
2	Infliximab	23	7	Hemophagocytic lymphohistiocytosis	22
2	Spectrum	21	7	Intravenous immunoglobulin	22
3	Cytokine profiles	62			

Due to the rarity of AoSD, many clinical studies are limited by small sample sizes and are thus underpowered. Furthermore, because of the varying clinical designs among different studies an accurate consensus is difficult to conclude. These are significant obstacles that need to be overcome to improve the credibility of published AoSD studies in the future.

LIMITATION

Analysis of AoSD article by Citespace and Vosviewer has some limitations. The first is the deadline for article retrieval by 2020, but as WoSCC continues to update, the number of articles retrieved in this study may be slightly different from the actual number of relevant articles. The Second, due to the possible time lag, the importance of some studies, especially some newly published article, may not be given sufficient attention at present. Finally, the use of single database WOSCC is also a limitation. However, its use can be further substantiated, as it provides more accurate document type labeling than other databases such as Scopus (44). And this research based on bibliometrics still well demonstrates the research hotspot and development trend of AoSD, especially

providing reference for young scholars in scientific decision-making.

CONCLUSION

This study analyzed AoSD research published from 1976 to 2020. Furthermore, we summarized the regional distribution, journal category, article citation, main cooperative groups, and keyword clustering related to AoSD research. As an understudied, orphan disease, the mechanisms and pathogenesis of AoSD still need to be elucidated. The development of targeted AoSD therapy is a relatively effective and safe. However, existing clinical research samples sizes are small and prone to Type I or Type II errors. It is necessary to further expand the clinical sample size and clarify the safety and effectiveness of biological agents. This study provides key insights into current AoSD research and can be used as a useful resource for researchers in the field to identify hotspots and trends.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

ACKNOWLEDGMENTS

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Effects of a Smoke-Free Policy in Xi'an, China: Impact on Hospital Admissions for Acute Ischemic Heart Disease and Stroke

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Background: Smoking and secondhand smoke (SHS) exposure rates are much higher in China than in other countries. A smoke-free policy was implemented in Xi'an, a city in Shaanxi Province, China, on November 1, 2018. This study aimed to evaluate the effect of the smoke-free policy on changes in hospital admissions for acute ischemic heart disease (AIHD) and stroke in Xi'an.

Methods: All subjects had been hospitalized for AIHD or stroke from February 9, 2017 to December 25, 2019 (study period: 150 weeks) in six randomly selected public hospitals out of 36 tertiary hospitals in Xi'an. A generalized additive model developed using an interrupted time series design was used to compare immediate and annual percent changes in hospital admissions before and after policy implementation.

Results: The study included 31,400 cases (16,656 cases of AIHD and 14,744 cases of stroke) from 6 hospitals in Xi'an. Immediately after implementation of the smoke-free policy, AIHD admissions were reduced significantly (−31.66%, 95% CI: − 39.45 to −22.86%), but stroke admissions were not (−4.94%, 95% CI: −13.26 to 4.17%). The annual reduction in stroke-related admissions (−14.54%, 95% CI: −23.53 to −4.49%) and the annual increase in AIHD-related admissions (40.58%, 95% CI: 22.08 to 61.87%) were significant. Although there was no significant reduction in AIHD admissions, stroke admissions were significantly reduced by −15.73% (from 7,350 to 6,194) after implementation of the smoke-free policy in Xi'an.

Conclusion: The smoke-free policy had different effects on hospital admissions for AIHD and stroke in Xi'an. Xi'an should improve its smoke-free legislation and expand the measures to maintain or achieve additional significant health benefits. These findings can guide the formulation and implementation of regional and national smoke-free policies.

Keywords: stroke, acute ischemic heart disease, second-hand exposure, tobacco, smoking, smoke-free policy

INTRODUCTION

In 2019, 341 million (30%) of the 1.14 billion tobacco smokers worldwide were located in China, and the age-standardized rate of smoking in China was 49.7% (318 million) for males and 3.54% (23.2 million) for females (1) In that year, Chinese tobacco consumption was 2,150 cigarette equivalents per person, which was much higher than that worldwide (1,110 per person). Consequently, the smoke-related deaths in China increased from 1.5 million in 1990 to 2.4 million in 2019, and a 57.9% increase in smoke-attributable deaths (1). China has implemented many measures in an effort to reduce smoking rates (i.e., the creation of smoke-free locations, local smoke-free policies), but the effects are very limited (1). Smoke-free policies provide short- and long-term health benefits mainly through reducing exposure to second-hand smoke (SHS) in the environment and reducing active smoking by encouraging cessation of smoking and increasing public awareness about the dangers of smoking (2).

The "Healthy China Program (2019–2030)" has the goal of reducing smoking rates to 24.5 and 20% among people over 15 years old by 2022 and 2030, respectively, and protecting 30 and 80% of the population with comprehensive smoke-free regulations (3). However, as of January 2022, there were only 20 100% smoke-free cities in China, and while 11 cities (Qingdao, Beijing, Lanzhou, Shenzhen, Shanghai, Xi'an, Hangzhou, Qinhuangdao, Wuhan, Zhangjiakou, and Xining) had specific smoke-free laws, this covered only 213 million people (15.1% of the total population) (4). Thus, the smoke-reduction goals seem unlikely to be met on schedule.

Studies on the health effects of a smoking ban on ischemic heart disease (IHD, including acute myocardial infarction, AMI) and cerebrovascular diseases (CVD, including stroke) have very different findings due to differences in the policy details and implementation degrees. For example, Spain's partial and comprehensive smoking ban did not significantly reduce hospitalizations for IHD or CVD (5). The national Irish smoking ban (6) was associated with immediate reductions in IHD (−26%) and stroke (−32%) mortality, but the annual effects were non-significant. The partial smoking ban in Hong Kong (7) significantly reduced the annual mortality due to IHD (−9.3%) but not that due to CVD. Even in the 100% smoke-free cities in China, AMI and stroke hospitalizations in Beijing (8) and Qingdao (9) still greatly differed in immediate and annual changes. Specifically, in Beijing, the stroke hospitalizations significantly decreased both immediately and annually, while AMI decreased only immediately; in Qingdao, the stroke hospitalization significantly decreased in annually, but AMI hospitalizations increased immediately with an annual decrease.

Xi'an implemented a comprehensive smoking ban on November 1, 2018 (10) However, the actual health effects of the smoking ban are still unclear. This study examined hospital admissions for acute ischemic heart disease (AIHD) and stroke in Xi'an before and after policy implementation to evaluate the health effects of the ban, fill gaps in the impact of smoking bans in Xi'an, and provide evidence for policy-makers to further improve and enforce measures in the future. We also hope that this study will provide reliable evidence for promoting national smoke-free legislation in China and provide clues to other countries.

MATERIALS AND METHODS

Materials

According to data accessibility, we selected 6 tertiary hospitals in Xi'an, accounting for about 16.67% of the tertiary hospitals. The study subjects were patients hospitalized for AIHD or stroke from February 9, 2017 to December 25, 2019, for a total of 150 weeks. Data were obtained from the electronic case registration systems of the 6 hospitals and determined based on the first discharge diagnosis according to the International Classification of Diseases, 10th revision (ICD10): AIHD (I20–I24) and stroke (I60–I64). The extracted information included age, sex, birth place, current residence, work address, admission time, discharge department, main discharge diagnosis code, main discharge diagnosis name, etc. Patients under the age of 15 years or who were not permanent residents of Xi'an (11) were excluded from this study. Patients who were admitted to the hospital repeatedly for the same disease within 28 days were also excluded; only the first admission within this period was retained.

Data on air pollution in Xi'an were obtained from the official website of the Shaanxi Provincial Department of Ecology and Environment (http://sthjt.shaanxi.gov.cn/), and the 24-h average temperatures (°C) and relative humidity (%), which represent the average levels in Xi'an, were obtained from the China Meteorological Data Sharing Service System (http://data.cma.cn/). Annual legal holidays (New Year's Day, Spring Festival, Qingming Festival, Labor Day, Dragon Boat Festival, Mid-Autumn Festival, and National Day) were determined according to the information issued by the General Office of the State Council of the People's Republic of China (http://www.gov.cn/zhengce/xxgk/index.htm). The population over 15 years of age in Xi'an was calculated based on the 2018–2020 Statistical Yearbook of Xi'an (http://tjj.xa.gov.cn/); this value was used to calculate the hospital admission rate and was an offset variable in the model to adjust for possible changes in the population over time. Ethical approval was granted by the Biomedical Ethics Committee of Xi'an Jiaotong University (No: 2020-1350).

Statistical Analysis

The outcomes of this study were the number of admissions for AIHD and stroke each week, and data spanned multiple time points before and after the intervention. Policy studies usually use an interrupted time series (ITS) design to assess whether "changes" in outcomes are attributable to the intervention by comparing the immediate and annual relative changes in outcomes following the intervention. Therefore, to test whether hospital admission rates for AIHD and stroke changed after the policy implementation, a generalized additive model (GAM) was developed using the ITS design. All variables in the model were analyzed as a time series in weeks. The cubic spline function was used to fit non-linear parameters such as the air quality index, average temperature and relative humidity. The number of legal holidays per week was also included in the model to illustrate differences between weeks. A preliminary analysis showed that

the long-term trend was linear. Therefore, time was included in the model as a linear variable to quantify the changes in population risk factors and other long-term trends. In addition, an interaction between the tobacco control policy and the time after the policy was implemented was also included in the model to estimate the change in the long-term trend slope between the pre- and post-policy periods. Seasonality was modeled by a Fourier series of sine and cosine terms (11).

The immediate relative change (percentage) in hospital admissions from the pre- to post-policy period was calculated as $100 (\exp(\beta_2)-1)$, which represents the change in admissions in a given week, and the annual relative change was calculated as $100(\exp (52*\beta_3) -1)$ (11). The number of people protected by the policy was defined as the difference between the number of admissions predicted by the model and the actual number of admissions. To assess the impact of the policy on different population subgroups, the data were stratified by age (<65 years old or ≥65 years old) and sex and analyzed in each subgroup. To further verify whether the final model detected the real effects of the smoke-free policy, a series of false intervention dates were created to test the robustness of the model. All analyses were conducted in R (V.3.5.1), (12) and the model was carried out with the "mgcv" package (13).

$$log (Y) = \text{offset} \log (P) + \beta_0 + \beta_1 T + \beta_2 Int + \beta_3 \left(Int * T'\right)$$
$$+ \beta_4 \cos(\frac{2T * \pi}{52}) + \beta_5 \sin(\frac{2T * \pi}{52})$$
$$+ \varepsilon + Holiday + s(X')$$

Where Y represents the weekly outcome variable, P represents the average population, and T represents the time since the start of the study; Int is a dummy variable representing whether the policy was implemented (before the policy was implemented, the value was 0, after the policy was implemented, the value was 1); T' represents the time after the smoke-free policy was implemented; β_0 represents the baseline level at T = 0, β_1 represents the model coefficient of the pre-policy time trend, β_2 is the coefficient when the intervention variable (policy) was implemented, indicating the immediate change of the policy, and β_3 indicates the long-term slope change following implementation of the smoke-free policy; sin/cos is the seasonal factor adjusted according to the Fourier function; Holiday is the statutory holiday; s is a smooth function; and X' are nonlinear parameters including air quality index, weekly average temperature and average relative humidity.

RESULTS

From February 9, 2017 to December 25, 2019, 31,400 cases (16,656 cases of AIHD and 14,744 cases of stroke) were admitted to 6 hospitals in Xi'an. The specific numbers of hospital admissions by sex and age subgroups are shown in **Table 1**. Males and elderly people (≥65 years old) had a larger number of hospital admissions for these two diseases than females and younger people. In terms of the average annual crude admission rates, stroke and AIHD admission rates in men were significantly higher than those in women in Xi'an.

TABLE 1 | Descriptive characteristics of AIHD and stroke hospital admissions in Xi'an by age and sex, n (%).

Age	Stroke		AIHD	
	Male (n = 9,529)	Female (n = 5,215)	Male (n = 9,261)	Female (n = 7,395)
≤64 years	4,125 (43.30)	1,607 (30.80)	4,805 (51.90)	2,719 (36.80)
≥65 years	5,404 (56.70)	3,608 (69.20)	4,456 (48.10)	4,676 (63.20)
χ^2	220.70		379.35	
P	**<0.001**		**<0.001**	

Bold indicates P value <0.05, which is statistically significant. AIHD, acute ischemic heart disease.

Figure 1 shows the monthly trends of hospital admission rates for AIHD and stroke. The rates were higher for AIHD, and the predicted trends increased markedly. As shown in **Figure 1**, there were seasonal patterns for the two diseases: the AIHD and stroke admission rates from October to December were much higher than those in other months.

Changes in Hospital Admissions

Figure 2 shows the model-fitted trends of the actual number of weekly hospitalizations for stroke and AIHD; the sex- and age-specific group trends are shown in **Supplementary Figures 1, 2**. The changes in hospital admissions for AIHD and stroke after implementation of the smoke-free policy in Xi'an on November 1, 2018 are shown in **Table 2**, with the set of adjusted variables. The immediate reduction in hospital admissions was approximately −31.66% (95% CI: – 39.45 to −22.86%) for AIHD, while the immediate reduction for stroke was non-significant (−4.94%, 95% CI: −13.26 to 4.17%). Additionally, regarding annual trends, the change in stroke hospital admissions was −14.54% (95% CI: −23.53 to −4.49%), while AIHD hospital admissions significantly increased by 40.58% (95% CI: 22.08 to 61.87%) (**Table 2**). The average percentage change in hospital admissions for the two diseases on a semester basis is provided in **Supplementary Table 1**.

The effects of the policy on the different sex and age groups are shown in **Table 2**. The hospital admissions for stroke did not immediately decrease significantly in any subgroup. Similarly, the annual female admissions for stroke did not significantly decrease (P > 0.05). The immediate AIHD admissions in each subgroup decreased significantly, while the annual AIHD admissions increased significantly.

We conducted additional sensitivity analyses to further verify our results. Overdispersion was found to be very limited, and we adjusted for it by following a "quasi-Poisson" distribution. Several false implementation dates were applied to test the impact of the policy on hospital admissions for the two diseases. We found that the false date results were not significant and that the magnitude of the change was smaller than the actual immediate change (**Supplementary Table 2**).
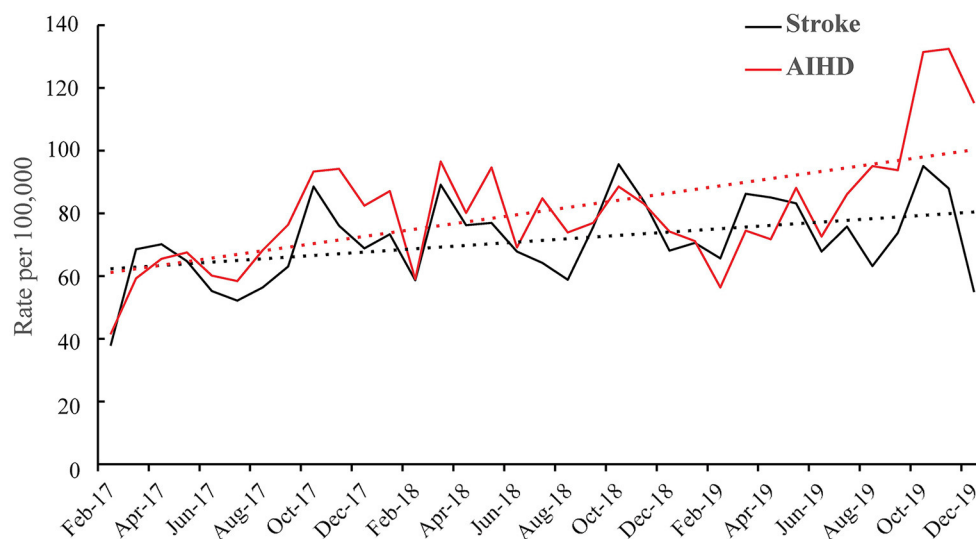
FIGURE 1 | Monthly hospital admission rates for AIHD and stroke and fitted linear trends from February 2017 to December 2019. The solid line represents the actual monthly admission rates, and the dashed line represents the fitted linear trend. Black represents stroke, and red represents AIHD. AIHD, acute ischemic heart disease.
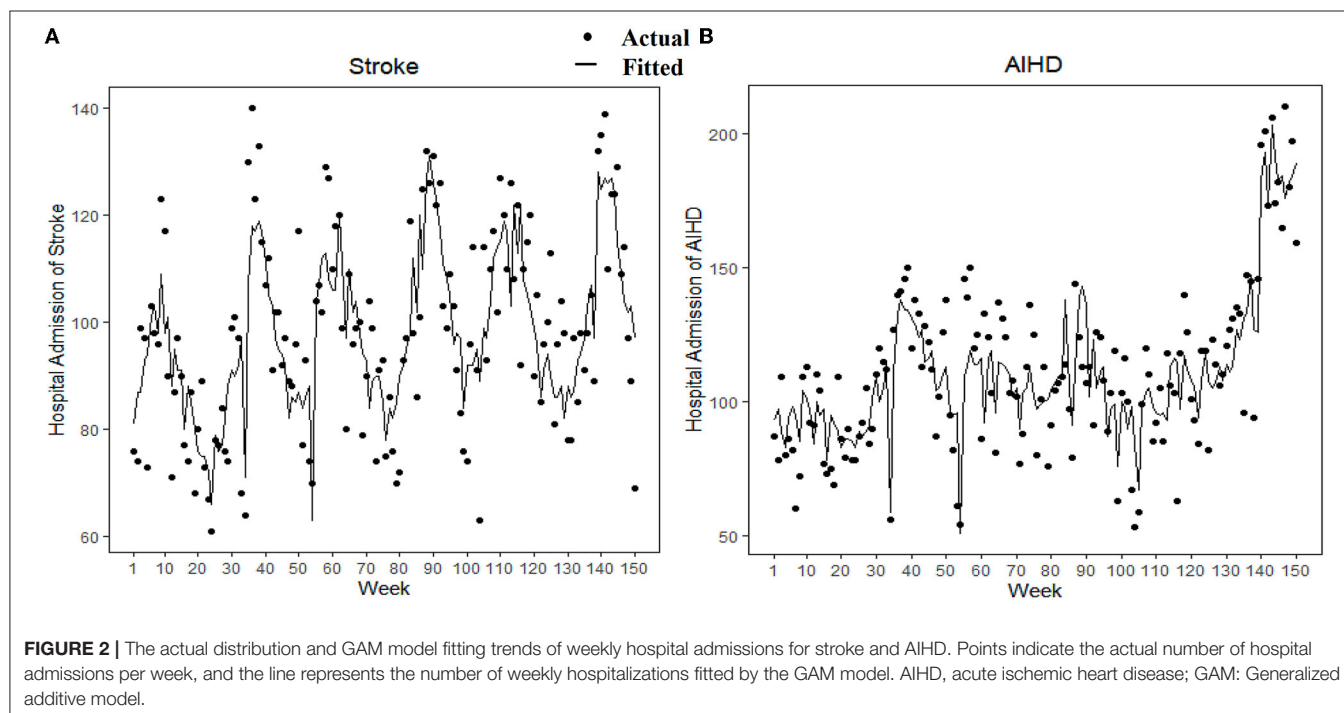
FIGURE 2 | The actual distribution and GAM model fitting trends of weekly hospital admissions for stroke and AIHD. Points indicate the actual number of hospital admissions per week, and the line represents the number of weekly hospitalizations fitted by the GAM model. AIHD, acute ischemic heart disease; GAM: Generalized additive model.

Protective Effect of the Policy Against Hospital Admissions

As shown in **Figure 3**, the protective effect of the policy was calculated as the difference between the predicted (red line in **Figure 3**) and observed hospital admissions (black line in **Figure 3**). The predicted and observed numbers of hospital admissions in the sex- and age-specific groups are shown in **Supplementary Figures 3, 4.** If the smoke-free policy was not implemented, hospital admissions for stroke and AIHD from November 1, 2018 to December 25, 2019 would have reached 7,350 (95% CI: 6362, 8,337) and 8,813 (95% CI: 7,258, 10,374), respectively. However, the actual hospital admissions for stroke and AIHD during this period were 6,194 and 7,273, respectively. Although there was no significant reduction in AIHD admissions, stroke admissions in Xi'an were reduced by −15.73% due to the smoke-free policy.

TABLE 2 | Average percentage change* (%) in hospital admission rates of all groups and sex- and age-specific subgroups due to the smoke-free policy in Xi'an, 2017–2019.

	Stroke		AIHD	
	Immediate change (95%CI)	Annual change (95%CI)	Immediate change (95%CI)	Annual change (95%CI)
Overall	−4.94 (−13.26 to 4.17)	**−14.54 (−23.53 to −4.49)**	**−31.66 (−39.45 to −22.86)**	**40.58 (22.08 to 61.87)**
<65years	−8.3 (−18.43 to 3.09)	**−14.58 (−25.92 to −1.49)**	**−33.65 (−43.03 to −22.73)**	**49.39 (24.99 to 78.56)**
≥65years	−4.72 (−14.79 to 6.54)	**−16.89 (−27.41 to −4.83)**	**−29.72 (−37.98 to −20.36)**	**31.17 (13.39 to 51.74)**
Male	−2.78 (−12.53 to 8.06)	**−14.53 (−24.67 to −3.04)**	**−30.15 (−38.82 to −20.25)**	**39.15 (19.19 to 62.45)**
Female	−11.33 (−22.19 to 1.04)	**−14.73 (−27.37 to 0.1)**	**−33.5 (−42.81 to −22.67)**	**44.04 (20.64 to 71.97)**

*Bold indicates P value <0.05, which is statistically significant. *, Adjusted for air quality index, legal holidays, population, seasonality, time trend, temperature and relative humidity. AIHD, acute ischemic heart disease; CI, confidence interval.*

FIGURE 3 | The predicted and observed hospital admissions for stroke and AIHD from February 2017 to December 2019. The red line represents the predicted hospital admissions without the smoke-free policy according to the GAM model; the black line represents the observed hospital admissions. AIHD, acute ischemic heart disease; GAM, Generalized additive model.
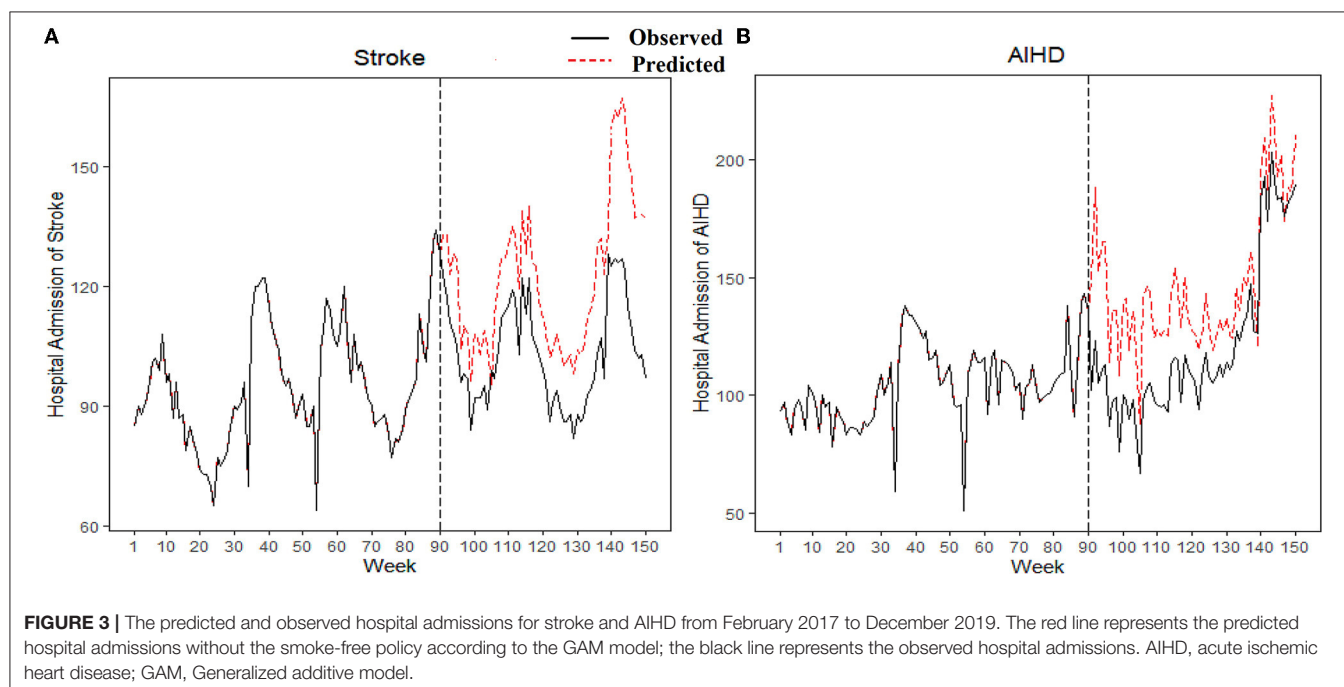
DISCUSSION

This study is the first to evaluate the comprehensive smoke-free policy in Xi'an. We randomly selected 6 hospitals with complete electronic medical record system data based on their geographic location. The dataset contained 150 time points, including 90 weeks before the policy was implemented. We excluded nonresident hospital admissions and adjusted for the air quality index, average temperature and humidity, legal holidays, time trends, seasonal trends, and possible population changes during this period. After analyzing 31,400 hospitalized patients in Xi'an from 2017 to 2019, we found that the implementation of the smoke-free policy in Xi'an differentially impacted AIHD and stroke in patients over 15 years old.

An exposure to tobacco smoke lasting between 20 min and 8 h increases platelet sensitivity and reduces the ability of the heart to receive and process oxygen. Long-term exposure to tobacco smoke can cause coronary vasospasm through abnormal vascular activity, thereby inducing cardiovascular and cerebrovascular

diseases (14, 15) Therefore, smoke-free policies can prompt not only short-term effects but also long-term health benefits (2) In Xi'an, the smoke-free policy clearly states that smoking is prohibited in indoor public places, public transport and outdoor areas in some public places (10).

The immediate changes in hospitalizations for stroke after implementation of the smoke-free policy were nonsignificant; however, the annual trend of stroke admissions decreased significantly (−14.54%, 95% CI: −23.53 to−4.49%). This result was consistent with those of studies in Beijing, (8) Qingdao, (9) and Arizona; (16) in contrast, studies in Chile (17) and the United States (18) showed no significant impact on stroke admissions. The disease burden caused by stroke in China is much higher than that in other countries; therefore, the health benefits of smoke-free policies on stroke may be more obvious in China (19, 20).

After Xi'an's implementation of the smoke-free policy, significant immediate decreases in AIHD admissions (−31.66%, 95% CI: − 39.45 to −22.86%) were observed, while the annual

AIHD admissions increased significantly (40.58, 95% CI: 22.08 to 61.87%). The immediate trend was consistent with that of studies in Beijing (8) and Ireland (6). However, the significant increase in the annual trend differed from the results of studies conducted in Germany, (21) Uruguay, (22) Spain (23) and Qingdao (9). These studies found that the annual cardiovascular disease admissions were reduced due to the implementation of smoke-free laws.

The immediate effects of smoking on IHD are greater and more drastic than those on stroke. A comparison of current smokers with non-smokers revealed that the hazard ratio (HR) for IHD is higher than that for stroke (1.60 vs. 1.32, respectively), (24) and even non-smokers who are exposed to SHS at home and at work have much higher risks of IHD than non-smokers not exposed to SHS (25 vs. 20%, respectively) (25). After a smoker quits smoking, their risk of cardiovascular disease begins to decrease almost immediately (26). Compared with current smokers, the HRs associated with ex-smokers were 0.71 for IHD and 0.84 for stroke (24).

Smoking is one of the most common risk factors for stroke in China, accounting for a relatively high proportion (31.7–47.6%) of stroke incidences and ranking 2nd among all risks (27). Therefore, the health effects of stroke may be more obvious than those of IHD, and the significant decrease in the annual stroke admissions also indicates the effectiveness of the tobacco control measures in Xi'an (28). However, the annual IHD admissions continued to increase, which may be related to the small proportion of tobacco in the etiology of IHD and continuous increases in other risk factors (29). High systolic blood pressure, high total cholesterol, diets high in sodium, diets low in whole grains and smoking were the five most common risk factors for IHD in China. Although smoking dropped from 4th place in 1990 to the 5th place in 2015, representing the largest decline in age-standardized IHD disability-adjusted life year (DALY) rates among these factors (−14.5%), the DALY rates of high systolic blood pressure and diets high in sodium continued to increase (30 and 4.1%, respectively) (29) Moreover, as independent risk factors for IHD, these factors may have synergistic effects with smoking (30, 31) and obscure the effects of smoke-free policies. (32) Residents of Xi'an, the capital of Shaanxi Province, have diets characterized by high sodium and low potassium contents, with daily sodium intake far exceeding the 5 g recommended by the World Health Organization (32) However, increasing the amount of potassium in salt and reducing sodium provides the greatest protection against CVD, a level of protection greater even than quitting smoking (32) In 2015, the prevalence of hypertension in Xi'an was 41.59%, and the dyslipidemia rate of people over 40 years old was 50.34%, both higher than the national average, especially for women (30, 31) With the accelerated aging process, the standardized mortality rate and number of deaths due to IHD in Shaanxi Province increased by 34.5 and 177.5%, respectively, from 1990 to 2015 (29) Therefore, it is difficult to reverse the continuous increase in IHD admissions in Xi'an by relying on only tobacco control policies. We even suspect that without the implementation of the tobacco control policy, the IHD admissions in Xi'an would be much higher.

Moreover, the differences in the annual trends may reflect the incomplete implementation of Xi'an's smoke-free policy, which has caused a rebound effect. A survey conducted in Xi'an in April 2019 found that the $PM_{2.5}$ and nicotine concentrations in restaurants were not significantly reduced (33) and that the concentrations were still higher than those in Beijing, (34) Hangzhou, (33) New Zealand (35) and Latin America (36) indicating that after policy implementation, the rate of exposure to SHS in Xi'an restaurants was higher than those in other domestic cities and other countries.

The smoke-free policies implemented in different regions result in large differences in health effects according to age (7, 8) and sex. The main reasons for these differences may be related to differences in social behaviors, smoking rates, SHS exposure rates or policy implementation among these groups (8). There were no significant differences in the immediate stroke admissions among the subgroups. However, the annual changes in stroke admissions were significant in all subgroups except the female subgroup. The immediate and annual changes in AIHD admissions were significant in both the age and sex subgroups, with a greater impact on the population under 65 and women. The results are consistent with those of studies in Kentucky, (37) Beijing (38) and Italy (39). Many studies have indicated that although there is no sex difference in the effects of smoking on stroke, female smokers have a 25% higher risk of IHD than men (24, 25). This may be related to the effect of smoking on menopause and the antiestrogen effects of smoking. (24, 40). Long-term heavy smoking has a greater impact on aortic sclerosis in women than in men (40) Data from Shaanxi Province (41) have shown that both the SHS exposure rate and the female smoking rate increased from 2010 to 2015 (49.46 to 65.79% and 1.60 to 2.28%, respectively). Moreover, the SHS exposure rates in women and people < 65 years old were higher than those in other populations (41, 42) The opposite AIHD trends in the subgroups also indicate that tobacco control policies were effective but have not been completely implemented. Female smoking is generally more harmful to family health than male smoking (24) Even in elderly women with definitive IHD, smoking cessation can improve survival and reduce reinfarction rates (40). Given the increasing smoking rate among women in Shaanxi Province and the low smoking cessation rate, (41) more attention should be given to female smokers during the implementation of tobacco control policies.

By September 30, 2019, more than 2,69,000 locations were subject to supervision and inspection in Xi'an, and more than 50,000 individuals and 21,000 units were ordered to rectify breaches in conduct (4) An investigation of SHS exposure in some indoor restaurants in Xi'an in April 2019 found that the number of posted non-smoking signs and the smoking incidence improved significantly after the policy was implemented (33) However, levels of fine particulates ($PM_{2.5}$) and nicotine in restaurants showed non-significant decreases (from 52.00 to 37.00 ug/m^3 and from 4.47 to 3.04 ug/m^3, respectively), (33) and concentrations of nicotine and SHS exposure in men's restrooms and private rooms of indoor restaurants (33) were much higher than those in Beijing (34) and Hangzhou (33) Therefore, the government of Xi'an still needs to further improve the implementation of this policy to expand the smoke-free environment.

Compared with other cities' smoke-free policies, (43, 44) the current smoke-free policy in Xi'an only bans tobacco, (10) not e-cigarettes; thus, other tobacco control measures also need to be improved (such as banning cigarette and e-cigarette advertising and the sale of cigarettes and e-cigarettes to minors on campuses) (44). However, the most critical aspect is that the punishment for illegal actions, both of individuals and places, is too mild (10, 43) (individuals [Xi'an vs. Beijing]:10 vs. 50–200 Chinese yuan [CNY] fine; units [Xi'an vs. Beijing]: 500–1,000 vs. 2,000–10,000 CNY fine) and does not deter smoking, which to some extent weakens the effectiveness of law enforcement. Thus, it is hoped that these issues will be addressed in the newly revised law.

This study has several limitations. First, our study did not verify the implementation of the smoke-free policy and the SHS exposure levels in Xi'an. Second, the disease type was determined by only the first discharge diagnosis, and patients who were not admitted to the hospital were not considered (such as those who died outside the hospital). Additionally, there are complex and close relationships between the incidence of AIHD and stroke, and it was difficult to identify misdiagnoses in the data given the existing data and resources. However, a study found that the estimated rates of IHD and stroke were only slightly affected due to the compensatory methods of misclassification at the population level (11). Moreover, the misclassification of the above two diseases is likely to have nothing to do with the implementation of the smoke-free policy, so it may not have significantly impacted the results. Third, regarding the availability of data, the patients in this study were from tertiary hospitals with relatively complete electronic medical records systems, and there may have been bias in the results. In addition, although potential time trends and other covariates were adjusted for in the analysis, due to the lack of information, some important variables were not controlled for, such as education level, obesity, population cholesterol levels, and influenza outbreaks.

The more comprehensive a law is, the greater its impact (45). However, China has made little progress in reducing smoking rates or introducing national smoke-free laws (1). Hundreds of millions of people will be protected from the dangers of SHS if comprehensive smoke-free laws are effectively enforced and indoor exposure is eliminated, preventing 6 million premature deaths related to smoking (46). Before the realization of national smoke-free legislation, Xi'an should continue to improve policy implementation, expand policy scope, and improve the environment by reducing SHS exposure.

CONCLUSIONS

The smoke-free policy in Xi'an had different effects on AIHD and stroke hospital admissions. The changes in AIHD admissions

may have been affected by various factors, such as incomplete implementation of the policy and related risks or diseases. Xi'an should continue to improve its smoke-free legislation and expand the scope of implementation to maintain or achieve additional significant health benefits. These findings are also important for the future formulation and implementation of regional and national smoke-free policies.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Biomedical Ethics Committee of Xi'an Jiaotong University (No: 2020-1350). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

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SUPPLEMENTARY MATERIAL

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Optimizing Spatio-Temporal Allocation of the COVID-19 Vaccine Under Different Epidemiological Landscapes

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An efficient and safe vaccine is expected to allow people to return to normal life as soon as possible. However, vaccines for new diseases are likely to be in short supply during the initial deployment due to narrow production capacity and logistics. There is an urgent need to optimize the allocation of limited vaccines to improve the population effectiveness of vaccination. Existing studies mostly address a single epidemiological landscape. The robustness of the effectiveness of other proposed strategies is difficult to guarantee under other landscapes. In this study, a novel vaccination allocation model based on spatio-temporal heterogeneity of epidemiological landscapes is proposed. This model was combined with optimization algorithms to determine the near-optimal spatio-temporal allocation for vaccines with different effectiveness and coverage. We fully simulated the epidemiological landscapes during vaccination, and then minimized objective functions independently under various epidemiological landscapes and degrees of viral transmission. We find that if all subregions are in the middle or late stages of the pandemic, the difference between the effectiveness of the near-optimal and pro-rata strategies is very small in most cases. In contrast, under other epidemiological landscapes, when minimizing deaths, the optimizer tends to allocate the remaining doses to sub-regions with relatively higher risk and expected coverage after covering the elderly. While to minimize symptomatic infections, allocating vaccines first to the higher-risk sub-regions is near-optimal. This means that the pro-rata allocation is a good option when the subregions are all in the middle to late stages of the pandemic. Moreover, we suggest that if all subregions are in the period of rapid virus transmission, vaccines should be administered to older adults in all subregions simultaneously, while when the epidemiological dynamics of the subregions are significantly different, priority can be given to older adults in subregions that are still in the early stages of the pandemic. After covering the elderly in the region, high-risk sub-regions can be prioritized.

Keywords: COVID-19, epidemiological landscapes, optimal vaccine allocation, policy decision, vaccination

INTRODUCTION

The rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered a public health and economic crisis worldwide. As of January 15, 2022, there have been more than 3.1 billion cases and 5.5 million deaths reported (1). To combat this crisis, authorities have implemented various non-pharmaceutical interventions according to local conditions. Both empirical analysis and mathematical modeling suggest that non-pharmacological interventions, particularly lockdown and strict quarantine measures (2–4), are essential to mitigate the spread of the virus in the short term. However, given the high socio-economic costs of such measures, a long-term solution—an effective and safe vaccine-remains urgently needed. With the successive implementation of mass vaccination campaigns, the huge demand for vaccines has left many countries and regions facing severe resource shortages and supply imbalances (5, 6). Optimizing the allocation of limited vaccines is an urgent and critical issue for all countries.

The mathematical models help to inform the public and policymakers about possible scenarios for the development of infectious diseases and the potential effectiveness of different intervention methods. The compartmental models can be easily used to simulate various interventions. Epidemiological parameters in these models and simulation results are easy to understand. Based on the characteristics of this COVID-19 pandemic, a series of extensions for the classical SIR model have been proposed, such as age-group separation (7, 8), the introduction of asymptomatic infections (9, 10), deaths (11), and immunity period (12), and the incorporation of graph-based spatial components (10, 13). The efficacy and effectiveness of most vaccines on various endpoints have been assessed through rigorous controlled clinical trials or observational studies, such as BNT162b2 (14, 15), ChAdOx1 (16), mRNA-1273 (17), and inactivated SARS-CoV-2 vaccine (18). The optimal allocation of vaccines involves three main dimensions: object, timing, and places. Most of such studies focused on to whom and suggested that vaccine should be prioritized to people by age and risk. For the individuals in a region, prioritized vaccination of the elderly is beneficial in reducing severe symptomatic infections and deaths, while vaccinating younger age groups first can minimize symptomatic infections (11, 12, 19–21). The research on the spatio-temporal allocation of vaccines can be divided into two parts. Some studies used mathematical models to evaluate the effectiveness of different allocation strategies (22–26). Another approach was using optimization algorithms to find the possible optimal strategy (27–29). In existing studies, only the allocation for the epidemiological landscape (mainly refers to epidemic dynamics in sub-regions in our work) of a region over a certain period was identified. This does help to address the vaccine allocation under the corresponding epidemiological landscape. However, epidemiological landscapes change over time, and different countries may face different epidemiological landscapes

when deploying vaccines. Once the epidemiological landscape changes, the effectiveness of the proposed vaccine allocation strategy will be difficult to guarantee, i.e., there may be other better allocation strategies (see the **Supplementary Materials**). The effect of spatio-temporal heterogeneity of epidemiological landscapes on vaccine allocation is ignored to some extent in previous studies. These studies lack the optimal deployment of vaccines under different epidemiological landscapes.

The current vaccine spatial allocation strategy usually allocates available doses to sub-regions in proportion to the size of their population (referred to as the pro-rata allocation). For policymakers, this strategy may be easier to implement. However, such a strategy that ignores epidemiological landscapes may not always maximize the population effectiveness of vaccines. In this view, we proposed a new model of vaccination allocation using a graph-based spatial model and an extended SIR-based temporal model. We simulated the epidemic dynamics in subregions during vaccine deployment sufficiently through this model to set up a variety of possible vaccination scenarios. The optimization algorithm was then run under different scenarios to independently minimize two metrics of infection and disease burden: proportion of cumulative infections and deaths prevented. We also evaluated vaccine allocation in combination with non-pharmacological interventions. In epidemiology, a non-pharmaceutical intervention (NPI) is any method to reduce the spread of an epidemic disease without requiring pharmaceutical drug treatments. Vaccination is a pharmaceutical intervention by definition. However, we believe that vaccination is often not administered alone, but in conjunction with other non-pharmacological interventions. The non-pharmaceutical interventions may affect the effectiveness of vaccination strategies. There, we introduced vaccination at different intensities of non-pharmaceutical interventions to investigate the variation patterns of optimal strategies in the context of different degrees of viral transmission.

METHODS

Vaccination Allocation Model
The vaccine allocation model consists of two components: an age-structured deterministic compartmental model to describe the temporal dynamics of infectious diseases within the sub-region and a graph-based spatial model to simulate the epidemiological landscapes that the region may face at the time of vaccination.

Age-Structured Deterministic Compartmental Model
We stratified individuals by 10-year age groups, in line with previous parameter estimation and data. We assumed subjects started susceptible to infection (S) and could become exposed but not yet infectious (E) after effective contact. After a latent period, exposed individuals developed an asymptomatic infection (A) or a symptomatic infection (I). Both symptomatic and asymptomatic infectious individuals had a certain probability of being detected (ID). Infectious

individuals eventually recovered (R) or died (D) depending on the severity of their symptoms. Among them, asymptomatic individuals did not die but recovered at a given rate. We also assumed that recovered individuals became susceptible again at a given rate, reflecting eventual loss of temporary immunity from the infection (30, 31). We used the previously estimated (32) contact matrix C with age structure and corrected for reciprocity (33) based on the existing demographic structure of the subregion (34), adapting it to each subregion.

We introduced a leaked vaccine into the model and tracked the vaccinated individuals by subscript v. Vaccination was available to susceptible and recovered individuals. We assumed that the vaccine can have two effects on the vaccinated individuals. First, they are less likely to be infected with the virus compared to unvaccinated individuals (this effect is expressed by V_e). Second, the vaccine can also reduce the probability of developing symptoms upon infection (referred to as V_p). Vaccine effect on COVID-19 disease is defined as reduction in the likelihood to develop symptomatic diseases upon exposure (referred to as V_{dis}). The relationship (35) among V_{dis}, V_e, and V_p is shown as follows:

$$V_{dis} = 1 - ((1 - V_e)(1 - V_p)) \tag{1}$$

A flowchart of the model is presented in **Figure 1**. The equations used in the model are as follows:

$$c_{ij} = w_h c_{ij|\text{home}} + w_w c_{ij|work} + w_s c_{ij|school} + w_o c_{ij|other} \tag{2}$$

$$\lambda_i = \beta m_i \sum_{j=1}^{9} c_{ij}(\partial(A_j + A_{v,j}) + I_j + I_{v,j})/N_j \tag{3}$$

$$\frac{dS_i}{dt} = -\lambda_i S_i + \mu(R_i + R_{v,i}) \tag{4}$$

$$\frac{dE_i}{dt} = \lambda_i S_i - \sigma E_i \tag{5}$$

$$\frac{dA_i}{dt} = (1 - p_i)\sigma E_i - (\gamma_A + \omega_A)A_i \tag{6}$$

$$\frac{dI_i}{dt} = p_i \sigma E_i - (\gamma_I + \omega_I)I_i \tag{7}$$

$$\frac{dID_i}{dt} = \omega_A A_i + \omega_I I_i - \gamma_{ID}ID_i \tag{8}$$

$$\frac{dR_i}{dt} = \gamma_A A_i + (1 - \delta_i)(\gamma_I I_i + \gamma_{ID}ID_i) - \mu R_i \tag{9}$$

$$\frac{dD_i}{dt} = \delta_i(\gamma_I I_i + \gamma_{ID}ID_i) \tag{10}$$

$$\frac{dS_{v,i}}{dt} = -(1 - V_e)\lambda_i S_{v,i} \tag{11}$$

$$\frac{dE_{v,i}}{dt} = (1 - V_e)\lambda_i S_{v,i} - \sigma E_{v,i} \tag{12}$$

$$\frac{dA_{v,i}}{dt} = (1 - (1 - V_p)p_i)\sigma E_{v,i} - (\gamma_A + \omega_A)A_{v,i} \tag{13}$$

$$\frac{dI_{v,i}}{dt} = (1 - V_p)p_i \sigma E_{v,i} - (\gamma_I + \omega_I)I_{v,i} \tag{14}$$

$$\frac{dID_{v,i}}{dt} = \omega_A A_{v,i} + \omega_I I_{v,i} - \gamma_{ID}ID_{v,i} \tag{15}$$

$$\frac{dR_{v,i}}{dt} = \gamma_A A_{v,i} + (1 - \delta_i)(\gamma_I I_{v,i} + \gamma_{ID}ID_{v,i}) - \mu R_{v,i} \tag{16}$$

$$\frac{dD_{v,i}}{dt} = \delta_i(\gamma_I I_{v,i} + \gamma_{ID}ID_{v,i}) \tag{17}$$

where c_{ij} is the number of individuals in age group j contacted by an individual in age group i, $c_{ij|\text{home}}$, $c_{ij|work}$, $c_{ij|school}$, and $c_{ij|other}$ are the number of contacts at home, work, school, and other locations, respectively, and w_h, w_w, w_s, and w_o are the weight of the contact matrix of the four locations, respectively. λ_i is the force of infection for an individual in age group i, β is the transmission coefficient, μ_i is the relative susceptibility to infection for age-i, and α is the relative infectiousness of asymptomatic infections. $1/\mu$ is the average length of immunity. $1/\sigma$ is the mean duration of latent period. p_i is the proportion of the symptomatic in age group i. $1/\gamma_A$, $1/\gamma_I$, and $1/\gamma_{ID}$ are the average recover time of the asymptomatic, symptomatic and detected, respectively. ω_A and ω_I are the detection rate (*via* contact tracing and testing) for asymptomatic and symptomatic infections, respectively. δ_i is the fatality of the disease for age-i individuals.

Graph-Based Spatial Model

Due to the spatio-temporal heterogeneity and uncertainty in the spread of infectious diseases and the implementation of

FIGURE 1 | The flowchart of the transmission model.

interventions, the epidemiological dynamics of sub-regions when deploying vaccines can be either similar (same early, middle or late stage of a pandemic) or very different (sub-regions at different times of the pandemic). We introduced into the model the times at which vaccination begins in sub-regions to set up a series of possible vaccination scenarios based on this phenomenon. Different scenarios represent different epidemiological landscapes, as shown in **Figure 2**. For sub-region k under scenario s, if vaccination starts on day t_k^s, it means that the virus has been transmitted for $(t_k^s - 1)$ days. Depending on the scenario, the times were randomly generated within a reasonable range. This will affect the initial status of each compartment, such as sub-regions that are in the early stage of the pandemic with a greater proportion of susceptible

individuals. We quantified the intensity of the intervention using the control reproduction number (R_c, defined as the average number of secondary COVID-19 infections produced by typically infected individuals in a susceptible population with control measures). The R_c values for sub-regions were also randomly generated within a certain range. We used these R_c values to estimate some of the parameters in the model that were relevant to non-pharmacological interventions. This means that these parameters may be different for different sub-regions. Full simulation details can be found in subsection Vaccination Simulation Scenarios.

We considered a baseline basic reproductive number $R_0 = 2.5$ (no interventions) to calculate the transmission coefficient β. We defined the next-generation matrix (NGM) as

FIGURE 2 | Example of the simulated prevalence of sub-regional symptomatic infections under different scenarios without vaccination. **(A)** Scenario 1 (All subregions are in the early stages of the pandemic). **(B)** Scenario 2 (All subregions are in the middle stages of the pandemic). **(C)** Scenario 3 (All subregions are in the late stages of the pandemic). **(D)** Scenario 4 (The epidemic dynamics of the subregions differ significantly).

$$NGM_{ij} = \beta m_i \sum_j c_{ij}(\partial d_A + d_I) \qquad (18)$$

R_0 is the spectral radius of the NGM (36). d_A and d_I denote respectively the length of time individuals spend in states A and I.

Risk Assessment of Viral Transmission in Subregions

The effective reproduction number (R_e, defined as the average number of secondary cases per infectious case in a population made up of both susceptible and non-susceptible hosts) was usually used to measure epidemic transmission. Its value will change as the pandemic proceeds, as some people may have gained immunity through infection or vaccination. It is not very desirable to use the effective reproduction number at a given moment in isolation when prioritizing resources. Policymakers need to look at the whole picture and use it alongside other indicators. As shown in Equation 19, we assessed the risk of transmission in subregions by the effective reproduction number and the prevalence of symptomatic infections.

$$r_k = RS_k + \eta IS_k \qquad (19)$$

where r_k is the risk of viral transmission in the sub-region k. RS_k and IS_k are the total effective reproduction number (sum of effective reproduction number over T (our time horizon) days) and the total prevalence of symptomatic infections (sum of symptomatic infections over T days) without vaccination in the sub-region k, respectively, both of which are normalized. Considering that R_e could better reflect the transmission risk, we assumed $\eta = 0.5$.

Optimization Algorithm

The main focus of our study was on time and space. Within the subregion, our optimizer would prioritize vaccine allocation to the elderly. This is in line with most current policies and is more ethical. Two objective functions were ultimately chosen: the proportion of cumulative symptomatic infections and deaths prevented 1 year (our time horizon) after vaccination initiation compared with the unvaccinated base case. The reason why we choose symptomatic infections is that these individuals are more infectious compared to asymptomatic infections, and minimizing symptomatic infections is better for controlling the further spread of the virus. Moreover, symptomatic infections are closely related to public health policy concern: the burden on the health system. Therefore, we believe that although policies tailored to reduce deaths are of great significance, there is still a need to optimize the allocation of vaccines for symptomatic infections. This can provide more insight and flexibility in the formulation of public health policy.

$$\min_X f(X) \qquad (20)$$

$$s.t. \begin{cases} \sum_k X_k = 1 \\ X_k N \le P_k \\ 0 \le X_k \le 1 \end{cases} \qquad (21)$$

where $f(X)$ is the objective function and X is the decision variable. X_k is the proportion of vaccines allocated to subregion k to the total available vaccines. P_k is the number of people in sub-region k and N is the total number of people in the region.

To increase the chances of approaching the global optimal solution, we combined coarse global search with genetic algorithm to explore the entire space of possible combinations of vaccine allocation. Before running the genetic algorithm, we performed coarse-grained grid search over the entire decision variable space, with a search step of 0.1. For example, a point in the grid is $X = (0,0.1,0,0,0.1,0.4,0.2,0.2,0,0)$, which represents the sub-regions 2, 5, 6, 7, 8 are allocated to 10, 10, 40, 20, and 20% of the available vaccines, respectively. Each grid point needed to satisfy the above constraints, if not, the grid point would be discarded. We evaluated the objective function on all feasible grid points and selected the best 25 points. The best 25 points obtained above and the pro-rata allocation vector were put into the initial population of the genetic algorithm, and the remaining individuals of the initial population were randomly generated by the genetic algorithm according to the constraints. It is worth noting that under high vaccine supply (60−100%), the selection of feasible grid points may be <25 due to the reduction in the number of decision variables that meet the constraints. If the vaccine supply reaches 100%, the only theoretically feasible decision variable is the pro-rata vector. In this case, all individuals of the initial population were randomly generated by the algorithm itself.

RESULTS

We partitioned the continental US into the 10 Standard Federal Regions (10 HHS Regions) established by the US Office of Management and Budget. The 10 HHS Regions are our study subjects. More information on the 10 HHS regions can be found in **Supplementary Materials**. Given the current V_{dis} data and the uncertainty in the specific V_e and V_p values, we evaluated the optimal use of 50 vaccines with specific effectiveness and coverage (V_{dis} ranging from 60 to 100% and vaccination coverage ranging from 10 to 100% of the total population, in in-crements of 10%). We set $V_e = 50\%$ while varying the value of V_p according to V_{dis}.

Our study included four categories of scenarios and three intensities of non-pharmacological interventions. We assumed that the intensities of the non-pharmacological interventions in subregions were close and set, [2.0,2.3], [1.5,1.8], and [1.2,1.4] for low, moderate, and high intensity non-pharmacological interventions, respectively. We assumed that sub-regions deployed vaccines at a certain rate per day (rollout speeds of 0.05% of their population per day) until the supply was exhausted. Since each country will have different vaccination rates, the at-once allocation would make the results more general. Therefore, we also used this method to determine

TABLE 1 | The values for the hyperparameters of the GA.

Hyperparameter	Value
Population size	350
Elite count	18
Crossover fraction	0.8
Mutation fraction	0.15
Stall generations*	250
Function tolerance*	10^{-6}

The algorithm stops if the average relative change in the best fitness function value over MaxStallGenerations is less than or equal to FunctionTolerance.

TABLE 2 | The values and source of parameters in the model.

Parameter	Value	Method
$1/\sigma$	6	(34)
$1/\gamma_A$	7	(3)
$1/\gamma_I$	7	(3)
$1/\gamma_{ID}$	15	(3)
α	0.5	(3)
ω_A	–	Estimated
ω_I	–	Estimated
$1/\mu$	365	Assumed
β	–	Calculated
m_i	[0.4, 0.38, 0.79, 0.86, 0.8, 0.82, 0.88, 0.74, 0.74]	(37)
p_i	[0.29, 0.21, 0.27, 0.33, 0.4, 0.49, 0.63, 0.69, 0.69]	(37)
δ_i	[0.00002, 0.00006, 0.00031, 0.0008 0.0015, 0.006, 0.022, 0.051, 0.093]	(38)
w_h, w_w, w_s, w_o	–	Estimated
$c_{ij\mid home}, c_{ij\mid work}, c_{ij\mid school}, c_{ij\mid other}$	–	(32)

the near-optimal strategy under different scenarios (see the **Supplementary Materials**). All simulations were performed on the Matlab 2021a platform. For the genetic algorithm, we used the global optimization toolbox provided by it. The implementation details and hyperparameters of the genetic algorithm are shown in **Table 1**.

Simulation Setup
Parameter Estimation
The values of most parameters in the model referred to previous studies, while some of the parameters related to non-pharmacological interventions were estimated using genetic algorithm. The decision variables of the genetic algorithm are all parameters to be estimated. The fitness value is the absolute value of the difference between the target R_c and the estimated R_c. The values of relevant parameters are shown in **Table 2**.

Vaccination Simulation Scenarios
The possible scenarios were divided into two main categories: epidemic dynamics in sub-regions are relatively close or different significantly. For the first category of scenarios, we built three

sub-scenarios (Scenarios 1, 2, and 3). Scenarios 1, 2 and 3 represent epidemiological landscapes with all subregions in the early, middle, and late stages of the pandemic, respectively, while scenario 4 represents that the epidemiological dynamics of the sub-regions are significantly different. The generation intervals of the times when sub-regions start vaccination under different scenarios are as follows:

$$
t_k^s \in \begin{cases} (p_a t_k^p, (p_a + l_w) t_k^p), & s = 1 \\ ((1 - \frac{1}{2} l_w) t_k^p, (1 + \frac{1}{2} l_w) t_k^p), & s = 2 \\ ((1 + p_a) t_k^p, (1 + p_a + l_w) t_k^p), & s = 3 \\ (0, t_k^l), & s = 4 \end{cases} \tag{22}
$$

$$
l_w = \begin{cases} 0.1, & s = 1, 2, 3 \\ 1, & s = 4 \end{cases} \tag{23}
$$

where t_k^s represents the time when vaccination begins in sub-region k under scenario s. t_k^p represents the expected timing of the pandemic peak in sub-region k. l_w is the scaling factor of the generation interval to control the degree of proximity of the epidemic dynamics among sub-regions. p_a ($0 < p_a < 1-l_w$) is used to determine the location of the interval. In scenarios 1 and 3, we adjusted the value of p_a and conducted multiple experiments to check whether the near-optimal vaccine strategy changed when the interval changed. t_k^l is the pandemic duration for sub-region k.

Uncertainty and Sensitivity Analysis of Model Parameters
We assumed that each parameter obeys a uniform distribution over its range of values. Latin hypercube sampling (LHS) was performed for the entire parameter space. The model was run 1,000 times to analyze the sensitivity of response function values to changes in a single input parameter using the partial rank correlation coefficient (PRCC) as an indicator. The results are shown in **Figure 3**.

These results suggest that COVID-19 can be controlled effectively in the population by some interventions such as wearing masks, maintaining social distance, or large-scale vaccination. We chose model parameters that were more sensitive to the objective functions as parameters to be estimated: weights of contacts at home, school and other locations, and detection rates for asymptomatic as well as symptomatic infections.

Near-Optimal Vaccine Allocation Differs for Different Epidemiological Landscapes
The near-optimal spatio-temporal allocation for the same scenario is nearly identical under different intensities of non-pharmacological interventions. In this section, we analyzed how the near-optimal strategy to minimize symptomatic infections changed for different epidemiological landscapes and present results under low-intensity non-pharmacological interventions.

Compared with no vaccination, both strategies substantially mitigated viral transmission in all scenarios, especially when vaccine coverage is relatively high. If $V_{dis}= 60\%$ and vaccine

FIGURE 3 | Sensitivity analysis of the main parameters of the model. Each plot shows the sensitivity of the corresponding response function value to changes in a single main input parameter of the model. The green (red) bars indicate sensitive (insensitive) and gray bars indicate results that are not statistically significant.

FIGURE 4 | Percentage of cumulative symptomatic infections averted for both strategies under different scenarios. When $V_{dis} = 60\%$ and low-intensity non-pharmacological intervention, the percentage of cumulative symptomatic infections averted for the near-optimal strategy (green) and the pro-rata strategy (purple). Bars represent the mean of multiple experimental results and error bars represent uncertainty intervals (UI).

coverage was 50%, the near-optimal strategy could avert 40% (UI: 37−43%), 17% (UI: 16−17%), 42% (UI: 33−57%), and 52% (UI: 43−62%) of symptomatic infections in the four scenarios on average, respectively (**Figure 4**). This suggests that mass vaccination can go a long way in alleviating the spread of COVID-19 and also emphasizes the importance of distributing vaccines as soon as possible. Because the population effectiveness of vaccination will diminish as the pandemic proceeds. The near-optimal strategy under scenarios 1 and 4 could provide more gain compared to other scenarios, averting up to 9% more ($V_{dis} = 60\%$, ~60% of vaccine coverage) and 15% more symptomatic infections ($V_{dis} = 60\%$, ~40% of vaccine coverage) at the greatest difference between the two strategies, respectively. In scenario 1, when the vaccine coverage was ~30−70%, it was optimal to vaccinate higher-risk sub-regions at high coverage, while the pro-rata allocation was close to the near-optimal strategy for other coverages (**Figure 5A**). In stark contrast, in Scenarios 2 and 3, the pro-rata strategy was close to optimal regardless of vaccine coverage and effectiveness (**Figure 5B**). The near-optimal vaccine

allocation is similar for scenarios 4 and 1, with the difference that the priority was also given to higher-risk sub-regions when vaccine coverage is less than 30% (**Figure 5C**). This may be since that in scenario 1, the risk of transmission in the sub-regions is not very different and the virus is rapidly spreading. All subregions require large amounts of vaccines to slow the further spread of the virus. While in scenario 4, some sub-regions are already in the middle and late stages of the pandemic. In the case of insufficient vaccines, the available doses can be allocated to the sub-regions in the early stages of the pandemic. Both strategies tended to perform similarly as vaccine effectiveness and coverage increased.

Near-Optimal Vaccine Allocation Changes With Objective Functions

Next, we investigated the effect of the vaccination objectives on the near-optimal strategy and present some of the results under moderate intensity non-pharmacological interventions. The near-optimal vaccine allocation for the two objective
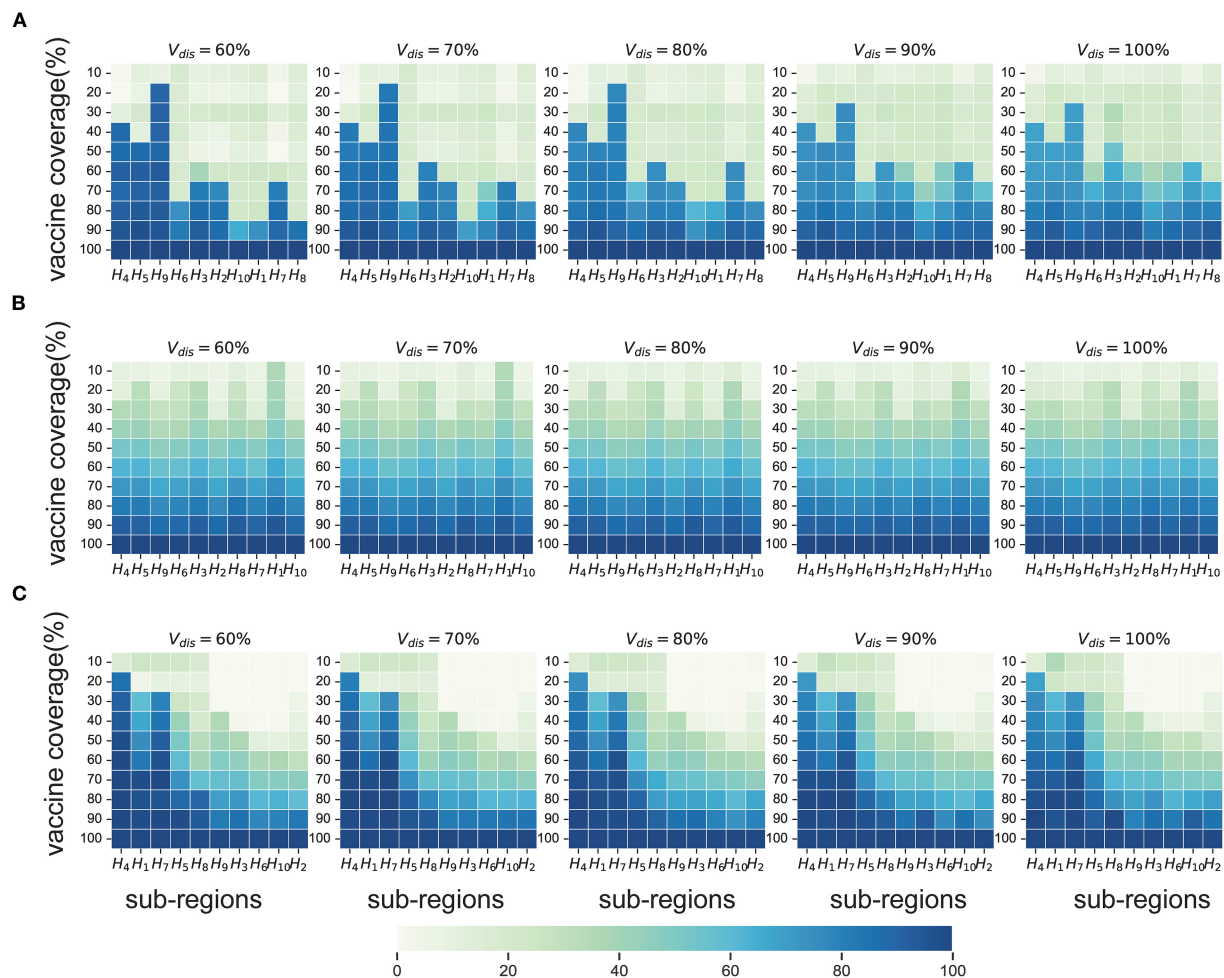
FIGURE 5 | Near-optimal allocation strategies to minimize symptomatic infections under scenario 1 **(A)**, 3 **(B)** and 4 **(C)**. For each heat map, each row from left to right is the decreasing direction of transmission risk, representing the total vaccine supply (percentage of the total population vaccinated) and each column represents a different subregion. Colors represent the percentage of the population in a sub-region to be vaccinated.

functions differed more in scenarios 1 and 4. While in scenarios 2 and 3, whatever the objective function was, the pro-rata allocation was close to optimal in most cases.

In Scenario 1, for low vaccine coverage, the near-optimal strategy to minimize symptomatic infections prioritized the coverage in higher-risk sub-regions; while when minimizing deaths, the optimizer's allocation results were similar to the pro-rata strategy. As more vaccines became available (30–60% vaccine coverage), the near-optimal strategy for symptomatic infections remained the same, while the near-optimal strategy for minimizing deaths first covered the elderly in all sub-regions as much as possible and then allocated the remaining dose to the subregion with the expected higher risk and coverage (**Figures 6A,C**). The main reason for this phenomenon is that the main contributors to the spread of the virus in this COVID-19 pandemic are the younger age groups, but the mortality rate in the elderly is much higher than in other age groups. In our optimizer, the vaccine is first distributed to the elderly in the sub-region. Allocating vaccine to older people in the region first helps to minimize deaths. The effective control of

the epidemic requires mass vaccination among young people. The near-optimal spatio-temporal strategy under scenario 4 is overall similar to that of scenario 1, except that with fewer vaccines available, the optimization algorithm may only focus on allocating vaccines to sub-regions in the early and middle stages of the pandemic (**Figures 6B,D**). In addition, we found that the gain from optimizing vaccine allocation to improve pro-rata strategy was relatively small when minimizing the deaths (**Figure 7**). This may be because prioritizing older adults is more beneficial for minimizing deaths within a sub-region than other vaccine prioritization strategies.

Effect of the Intensity of Non-pharmacological Interventions on Vaccine Allocation

Since the epidemic dynamics of the subregions in each experiment were randomly generated, the epidemiological landscapes under scenario 4 may vary considerably under different intervention intensities. Therefore, we only discuss the

FIGURE 6 | Near-optimal allocation strategies for different objective functions. Here, we only show the results for V_{dis} = 60 and 80%. **(A)** The near-optimal strategies to minimize symptomatic infections in scenario 1. **(B)** The near-optimal strategies to minimize symptomatic infections in scenario 4. **(C)** The near-optimal strategies to minimize deaths in scenario 1. **(D)** The near-optimal strategies to minimize deaths in scenario 4. For each heat map, each row from left to right is the decreasing direction of transmission risk, representing the total vaccine supply (percentage of the total population vaccinated) and each column represents a different subregion. Colors represent the percentage of the population in a sub-region to be vaccinated.

FIGURE 7 | Percentage of cumulative symptomatic infections **(A)** and deaths **(B)** averted for both strategies. Solid lines with solid circles and dashed lines with hollow circles represent the near-optimal and pro-rata strategies, respectively. For clarity, we highlight 1 set of results in **Figure 6** in each scenario. The shaded areas represent the range of effectiveness of strategies under multiple epidemiological landscapes simulated.

effect of the intensity of non-pharmacological interventions on the near-optimal vaccine allocation for the first 3 scenarios.

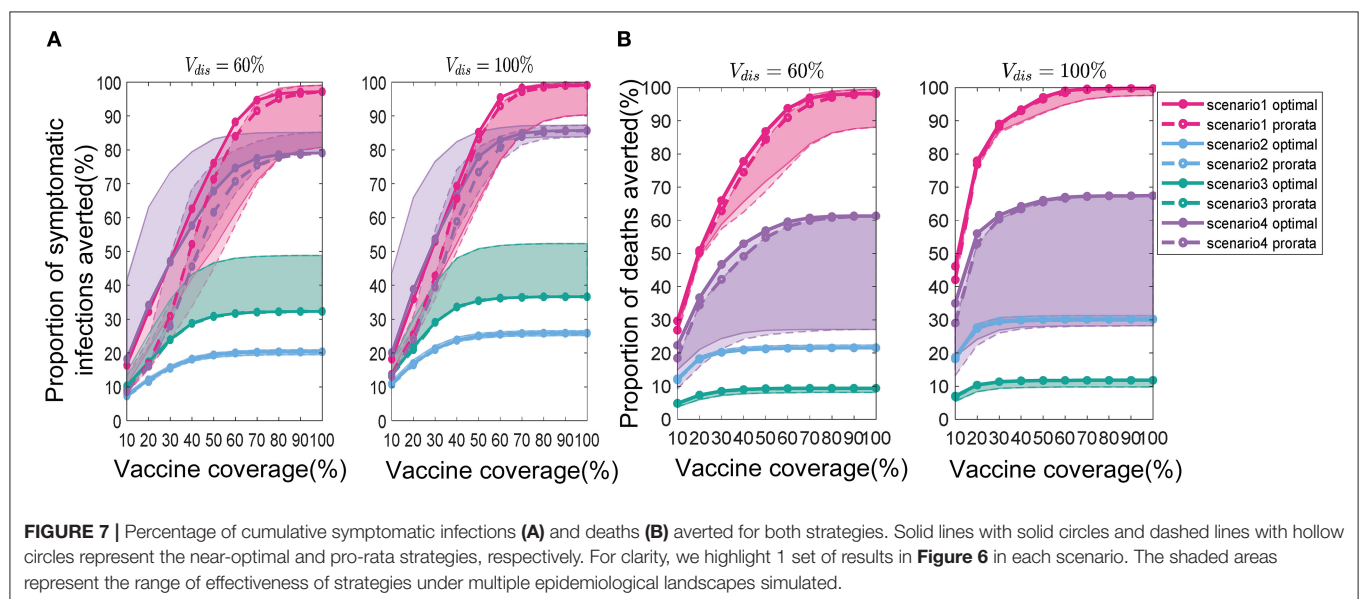We found that the intensity of non-pharmacological interventions had a greater effect on the near-optimal strategy under scenario 1. As the intensity of non-pharmacological interventions increased, the effectiveness of both strategies improved to varying degrees compared with no vaccination (**Figure 8**). For example, when $V_{dis} = 60\%$ and the total vaccine coverage was 50%, the near-optimal strategy in scenario 1 could prevent 43% (UI: 37−43%) of symptomatic infections if low-intensity non-pharmacological interventions were implemented along with vaccination. The symptomatic infections averted under moderate or high intensity non-pharmacological interventions would increase to 76% (UI: 51−76%) and 99% (UI: 96−99%), respectively (**Figure 8A**). While the effectiveness of the pro-rata strategy increased from 36% (UI: 34−36%) to 71% (UI: 45−71%) and 98% (UI: 87−99%; **Figure 8A**). The implementation of high-intensity non-pharmaceutical interventions not only increases the population effectiveness of vaccination but also requires fewer vaccines to control the epidemic. Vaccinating everyone in scenario 1 would still be difficult to completely control the outbreak under low-intensity non-pharmaceutical interventions. However, under high-intensity interventions, only 50% of the population would need to be near-optimally vaccinated to control the pandemic. Furthermore, when non-pharmacological interventions were
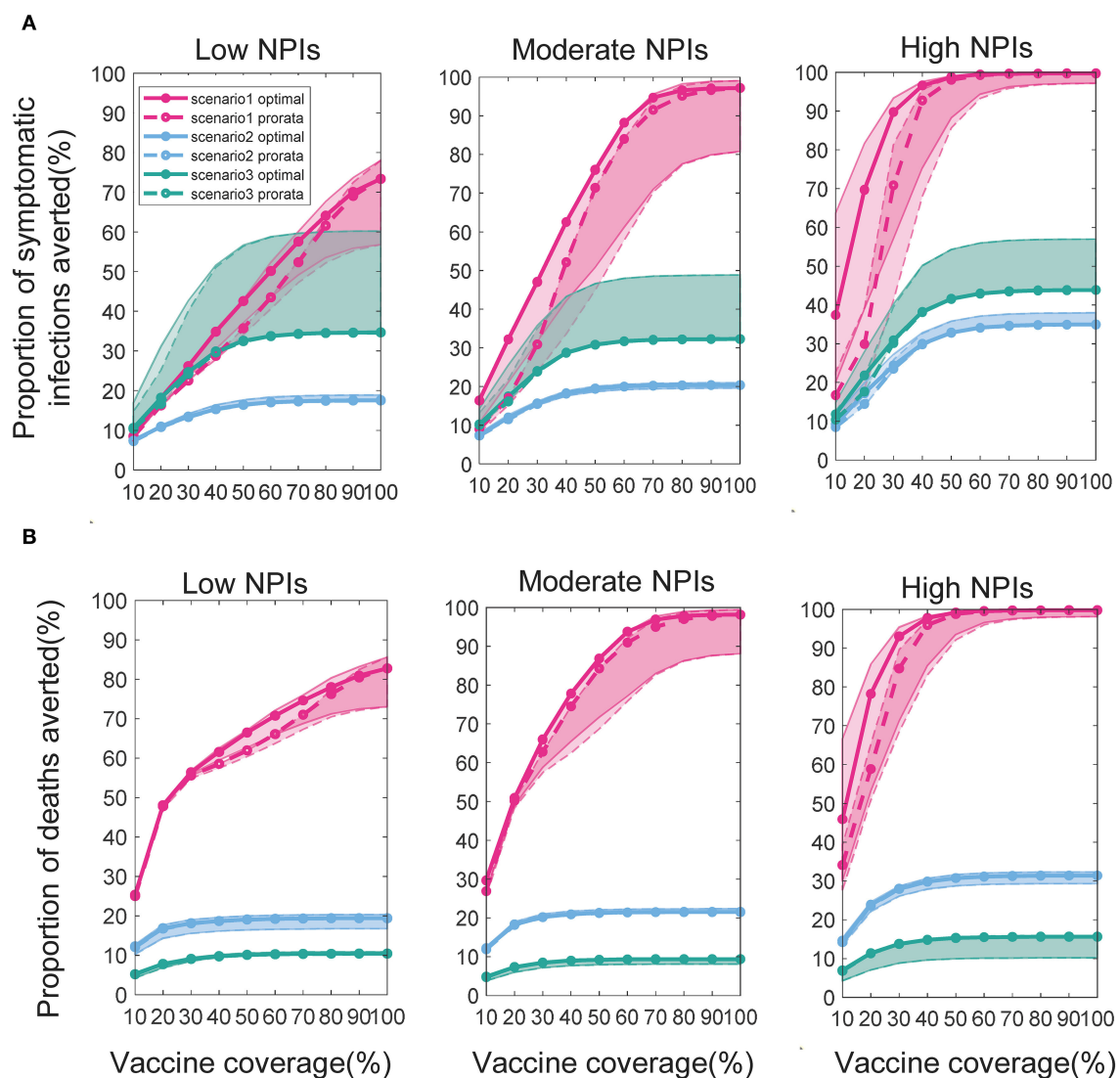
FIGURE 8 | Percentage of cumulative symptomatic infections **(A)** and deaths **(B)** prevented under different intensities of interventions. When $V_{dis} = 60\%$ and vaccine coverage is 10−100% of the population, the percentage of cumulative symptomatic infections and deaths prevented for the near-optimal (solid line with solid circles) and pro-rata (dashed line with hollow circles) strategy. For clarity, we highlight 1 set of results in each scenario. The shaded areas represent the range of effectiveness of strategies under multiple epidemiological landscapes simulated.

intensified, the optimizer tended to allocate vaccines more evenly across all sub-regions. For the same vaccine effectiveness and coverage, the range of optimal vaccine coverage for sub-regions decreased with increasing intensity of the non-pharmacological interventions, especially when the goal of vaccination was to minimize cumulative symptomatic infections and vaccine effectiveness and coverage were not sufficiently high (**Figure 9**).

DISCUSSION

The COVID-19 pandemic is not only a serious threat to human life and health but also has a huge impact on economic development and social stability. Non-pharmacological interventions are effective in reducing the incidence of COVID-19 cases. However, in the long term, these measures are difficult to implement consistently and large-scale vaccination is highly desirable. However, during the actual deployment of the vaccine, the demand for the vaccine may far outweigh the supply. Therefore, optimizing the allocation of limited vaccines makes good practical sense and can provide valuable information for policy formulation. In this work, we proposed a novel vaccine spatio-temporal allocation model that can reproduce the epidemiological landscapes that the region may face when deploying vaccines. We used this model and optimization algorithms to determine near-optimal vaccine spatiotemporal allocation strategy in different scenarios. Our findings suggest that the performance of vaccine spatiotemporal allocation strategies is driven by several complex factors, including vaccine effectiveness and coverage, epidemic dynamics of subregions when allocating, and non-pharmacological interventions implemented.

Based on the experimental results, we provide the following recommendations for vaccination policy. If all subregions are in the middle or late stage of the pandemic when the vaccine is deployed, the existing pro-rata strategy is desirable, regardless of vaccine effectiveness and coverage. This is because under such epidemiological landscapes, for both vaccination targets, the

gains from optimizing vaccine allocation are minimal compared to the pro-rata allocation. When sub-regions are in the same period of rapid virus transmission or when the epidemic dynamics of sub-regions differ significantly, prioritizing the higher-risk sub-regions may be more beneficial in controlling further virus transmission. While to minimize the deaths in the region, the elderly in all subregions need to be vaccinated as soon as possible. Under scenarios 1 and 4, the gain from optimizing vaccine allocation to improve pro-rata strategy was relatively small when minimizing the deaths. When the vaccine coverage is less than 30%, the effectiveness of the two strategies is almost the same under scenario 1. Based on this phenomenon, we suggest that older adults in all subregions should be vaccinated simultaneously if all subregions are in a period of rapid virus transmission, while older adults in subregions still in the early stages of a pandemic could be vaccinated first when the epidemiologic dynamics of each subregion differ significantly. After covering older adults in that region, priority can be given to high-risk subregions. In addition, our results suggest that the synergistic implementation of multiple pandemic interventions can lead to better pandemic control and that enhanced non-pharmaceutical interventions can reduce vaccination pressure. If non-pharmaceutical interventions are enhanced when deploying vaccines, the optimization strategy will tend to allocate the vaccine more evenly across subregions. This means that vaccines can be allocated more evenly across sub-regions based on the above recommendations to further enhance the effectiveness of vaccination if public health officials can encourage or urge the public to maintain good self-protection habits while vaccinating.

It is worth noting that this work still has certain limitations. First, the model assumed that the vaccine provided equal protection to all vaccinated individuals and that the effect was constant over the simulated time. Nevertheless, there may be some differences in the protective effect of the vaccine in different age groups, and asymptomatic infected individuals may result in weaker protection (39). The protective effect of artificial
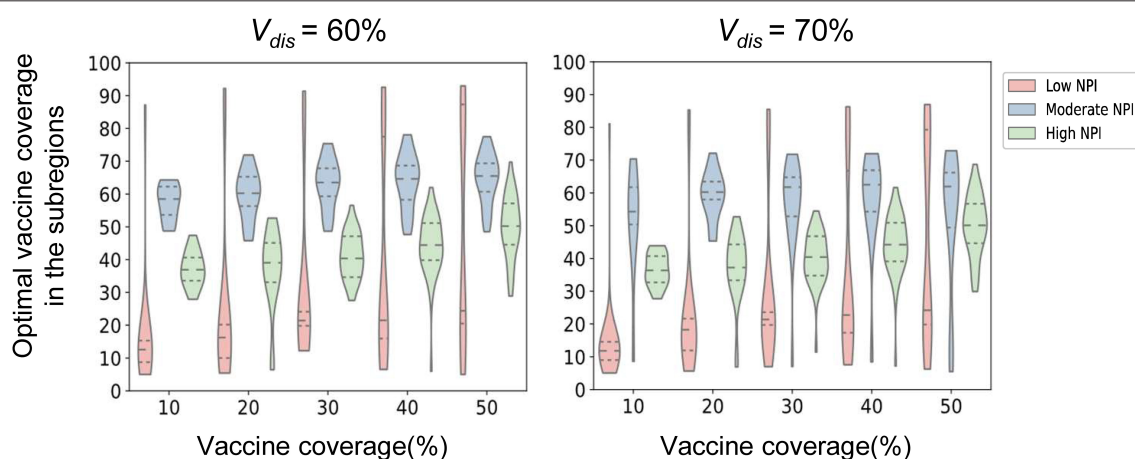

FIGURE 9 | Near-optimal vaccine coverage in sub-regions. Each violin represents the distribution of the primary optimal vaccine coverage for all sub-regions in scenario 1 when minimizing the number of symptomatic infections for a certain intensity of non-pharmaceutical intervention.

immunity induced by vaccination may decline over time (40). If immunity is transient, then these results will apply only for that duration. Second, the same rollout speed may be less desirable, so different rollout speeds for subregions may be the focus of our subsequent study, such as a faster rollout of vaccines in sub-regions with more supply.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://zenodo.org/record/6574113#.You7Ke5BxPY.

AUTHOR CONTRIBUTIONS

WC and JZ designed research and conceived the experiments. WC, JZ, and HD conducted the experiments and analyzed the results. WC, JZ, and XW contributed to the drafting of the work. WC, JZ, XW, XT, YT, and ZM contributed to the review and editing of the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.921855/full#supplementary-material

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Community Health Nursing in Iran: A Review of Challenges and Solutions (An Integrative Review)

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Background and Objective: In recent decades, nursing has witnessed many changes in Iran. Despite the numerous advances in nursing, the health system faces many challenges in community health nursing. This study aims to review the challenges in community health nursing in Iran and provide an evidence-based solution as well.

Materials and Methods: This article is an integrated review of the literature regarding the challenges in community health nursing published between 2000 and 2021 in the databases Scopus, Medline, Cochrane Database of Systematic Reviews, Science Direct, Google Scholar, Scientific Information Database (SID). After performing searches, 20 articles were selected and studied. Data analysis was done using Russell approach (2005).

Findings: The results of this study were summarized in 6 themes consisting of challenges in community health nursing education, practical challenges in community health nursing, policy-making challenges in community health nursing, management challenges in community health nursing, and infrastructural and cultural challenges. Solutions were also proposed to address each of the above issue.

Conclusions: The results of the study showed that diverse challenges exist in community health nursing in Iran, considering that community health nurses play an important role in providing primary health care and community-based care. In order to solve these challenges, the authors have some recommendations: modifying the structure of the health system with the aim of moving toward a community-oriented approach from a treatment-oriented one, developing laws to support community health nurses, creating an organizational chart for nurses at the community level, modifying nursing students' training through a community-based approach, and covering community-based services and care under insurance.

Keywords: community health nursing, nursing problems, challenges, solutions, Iran

INTRODUCTION

An examination of nurses' status and position in the service provision system around the world shows that nurses constitute the largest group of health care workers (1, 2). Community health nurses are a major link between the community and health institutions. They are able to understand and interpret the needs of the society and the objectives of health policymakers (3, 4). In addition, community health nurses have an excellent position and status for addressing many challenges in the health system including immigration, bioterrorism, homelessness, unemployment, violence, obesity epidemic, etc. (1, 2, 5). From the perspective of the World Health Organization (WHO) and the American Nursing Association, community health nursing is a special area of nursing that combines nursing skills, public health, and a part of social activities with the aim of promoting health, improving physical and social condition, and rehabilitation and recovery from diseases and disabilities (6, 7). Considering the importance of nursing services in the health service provision system and their role in universal health coverage, in the 66th Session of the health ministers of WHO Regional Office for the Eastern Mediterranean, much attention was devoted to developing plans for improving and strengthening community health nursing (8).

In all developed countries, community health nursing has had a significant growth in the health care system (9). In Canada, the community-based community health nursing has been established in 1978, aiming to maintain and promote the health of individuals, families, and communities. It also participates in the family physician and primary health care delivery (10). In some European countries, including Norway, Finland, the United Kingdom, Ireland, Sweden, and France, community health nurses have replaced physician-centered and hospital-centered approaches, providing health services for the members of the community (4, 9, 11–13). A study conducted by WHO on community health nursing's status in some less developed and developing countries (Bangladesh, Indonesia, Nepal, Cameroon, Senegal, Uganda, Guyana, Trinidad and Tobago) shows a lack of commitment and the low capacity of the policymakers to implement global and regional political tools regarding community health nursing, although most of the countries under study had a basic and operational framework for the optimal activity of community health nurses. On the other hand, only 6% of the community health nurses in these countries worked in the field of health promotion, disease prevention, and rehabilitation care, while this sector is supposed to be their main field of activity. The existing barriers preventing community health nurses from playing their role in developing countries include the lack of consensus in the realm of community health nursing practice, the lack of necessary coordination for inter-professional activities, few job opportunities for community health nurses, insufficient recognition of community health nursing, and great emphasis on clinical care in health centers (6). In Asian countries, including Japan, China, and Malaysia, community health nurses play a key role, too, focusing on the assessment of community health needs, health care delivery, and health promotion (9, 14, 15).

Iran is a populated country in the Eastern Mediterranean region, where health services are provided at public, private, and charity sectors (16, 17). In Iran, since 1958, behavioral and social sciences have been included in the nursing program as a major part of its curriculum. Then, in 1986, the disciplines of community-based and community-oriented nursing were considered by educational policymakers, followed by the inclusion of community health nursing and epidemiology courses in the undergraduate curriculum. Community health nursing program is developed in line with health-oriented policies and focuses on community health. Graduates of this field work in different settings of community by combining the nursing science with other health-related sciences and evidence-based practice (18, 19). Due to its focus on health promotion, the position of this discipline in the country's health system is very crucial, and is a major contributor to directing the community toward the 20-Year National Vision and in an ideal position to address the countless challenges against the health system (2). However, the role of nurses in Iran has not made significant progress and is limited to providing services in medical centers (20), because the viewpoint and the attitude of most Iranian health authorities is based on the employment of nurses in the secondary level of prevention, i.e., clinical care in hospitals (2). Therefore, hospitals are the most common setting for community health nurses' activities (21). Comprehensive health centers are also managed to provide health services by the workers with bachelor's and associate's degrees in family health, environmental health, occupational health, and disease control, as well as midwives. These services are provided sporadically in health service centers (18) and no effective strategies tailored to the needs of the community are adopted in order to provide care (22).

It is noteworthy and interesting that also in the family physician team, no position has been defined for community health nurses and most of the Iranian health authorities believe that nurses cannot provide significant health services (18). However, the community health nurse can be a complementary project in the family physician program and even make up for its shortcomings. This can help the government understand the *health for all* as a goal, the proof of which is the presence of nurses in blood pressure screening program in 2012 (23). On the other hand, numerous studies indicate community health nurses' abilities and their key role in identifying health needs and promoting community health (24–28). Although the education and training of community health nurses is costly for the government, their expertise is not utilized. At present, the services of community health nurses in Iran are mainly provided at the third level and at hospitals, because no position is defined for them in comprehensive health centers (18, 29). In other words, they have no defined job position to work in this field, although in the curriculums, the future job status of this discipline is designed (30). Therefore, one of the most important infrastructural issues is to create a position and a job description in the organizational chart for community health nurses in comprehensive health centers (31).

A brief review shows that studies in Iran have mostly focused on the challenges of community health nursing education and barriers against home care (1, 16, 18, 19, 32–34) and other

aspects of community health nursing have rarely been studied. In addition, no study has been conducted to offer solutions for addressing the challenges of community health nursing. Although other studies have been conducted in different cultures and contexts, an integrated review of them can help identify and eliminate present barriers with the aim of facilitating future planning and policymaking to enhance the status of community health nursing. Therefore, by conducting an integrated review, the present study aimed to identify the challenges of and barriers against community health nursing and the strategies to address them.

METHODOLOGY

This is an integrative review study on the challenges of community health nursing and the related solutions. The integrated review of literature is the summarization of previous studies by extracting the study results. This method is used to evaluate the strength of scientific evidence, identify gaps in current research, detect the needs for future research, create a research question, identify a theoretical or conceptual framework, and explore the research methods that have been successfully used. The integrative review study is based on Russell model which consists of 5 steps as follows: (1) formulating the research problem, objective, and question, (2) collecting data or searching through articles, (3) evaluating data, (4) data analysis, (5) interpreting and presenting the results (35).

Formulating the Research Problem, Objective, and Question

Considering the items discussed in the introduction, this study is conducted to determine the challenges of community health nursing in Iran and the related solutions. Two key questions guiding the review process include "What are the challenges of the community health nursing discipline in Iran?" and "What are the solutions to address these challenges?" Answering these two key questions will help detect the challenges of community health nursing, propose solutions to address them, and promote the community health nursing discipline.

Collecting Data or Searching Through Texts

In this study, the target population consisted of all the studies (articles and dissertations) that had been conducted in the field of community health nursing regarding its challenges, barriers, and solutions, the full texts of which were accessible. Available resources, including all the studies on the challenges of community health nursing, were reviewed in this study. A comprehensive search was done through the databases Medline, Scopus, Cochrane Database of Systematic Reviews, Science Direct, Google Scholar, and Scientific Information Database (SID) for the papers published between 2000 and 2021 in eligible English or Farsi journals.

The keywords that were searched consisted of community health nurse, community-based nursing, public health nurse, nursing challenges, nursing position, and primary health care. The keywords were investigated both separately and in combination with each other (**Table 1**). Finally, after preforming the search, 142 published articles were identified.

Data Evaluation

The relevant articles were evaluated based on the title, abstract, text, as well as the inclusion and the exclusion criteria. The inclusion criteria for the studies consisted of the following: (1) examining the challenges of and barriers against community health nurses and its position, (2) containing the keywords or their equivalent in the title or abstract of the article (3) Being written in either Farsi or English. The exclusion criteria included the following: (1) not accessing the original paper and the information on its methodology, (2) being written in other languages, (3) being irrelevant to the research question. It is noteworthy that in this study, there were no limitations in terms of research method, so that the results of various studies could be used.

Selecting Studies

After doing the systematic search, the studies related to the search keywords were found. After removing the duplicate titles (79 articles), the title, the abstract, and the full text of the studies were reviewed by the research team, and the inclusion and the exclusion criteria were applied. Twenty-four articles were excluded due to being irrelevant and 55 articles entered the screening stage, 20 of which were excluded. Then 35 articles were examined regarding eligibility and, finally, 20 articles were included in the study. The studies were selected by a research team consisting of two nursing professors (faculty members of Ahvaz Jundishapur University of Medical Sciences and Tehran's Shahid Beheshti University of Medical Sciences) and one nursing PhD student (Ahvaz Jundishapur University of Medical Sciences). Furthermore, the research team came to a consensus through more discussion regarding the points of disagreement.

Data Analysis

At this stage, the articles were reviewed separately. Finally, 20 articles related to the purpose of the study were reviewed and analyzed. Each article was read completely and the results of the studies were extracted from them. After extracting the results of the articles, their results and statistical analysis were compared. The results with the highest frequency in these articles were further interpreted in the next phase.

Interpreting the Data and Publishing Information

At this stage, according to the analysis of the related studies, their comparison, and the data frequency, the following items were extracted.

RESULTS

Search Results

After eliminating the duplicate articles ($n = 79$), 55 studies entered the screening phase and their titles and abstracts were

TABLE 1 | Search strategy.

Databases	Searched outcomes	Inclusion criteria
• MEDLINE • Science Direct • Scopus • Google Scholar • Cochrane Library • CINAHL • Scientific Information Database	• Community Health Nurse • Community Based Nursing • Public Health Nurse • Nursing Challenges • Nursing position • Primary health care • Universal Health Coverage • Search terms were specified with the Boolean expression *AND(work OR job)*	• Peer-reviewed publications • January 2000- December 2021 • Being written in either English or Persian • Containing the keywords or their equivalent in the title or abstract of the article
Results database search after exclusion of duplicates	77	**Exclusion criteria** • Not accessing the original paper and the information on its methodology • Being written in other languages
Results manual search	2	
Total identified studies	79	
Removed based on title or abstract	24	
Removed after in-depth reading	35	
Final selection of included articles	20	

FIGURE 1 | PRISMA flowchart for search strategy and results.
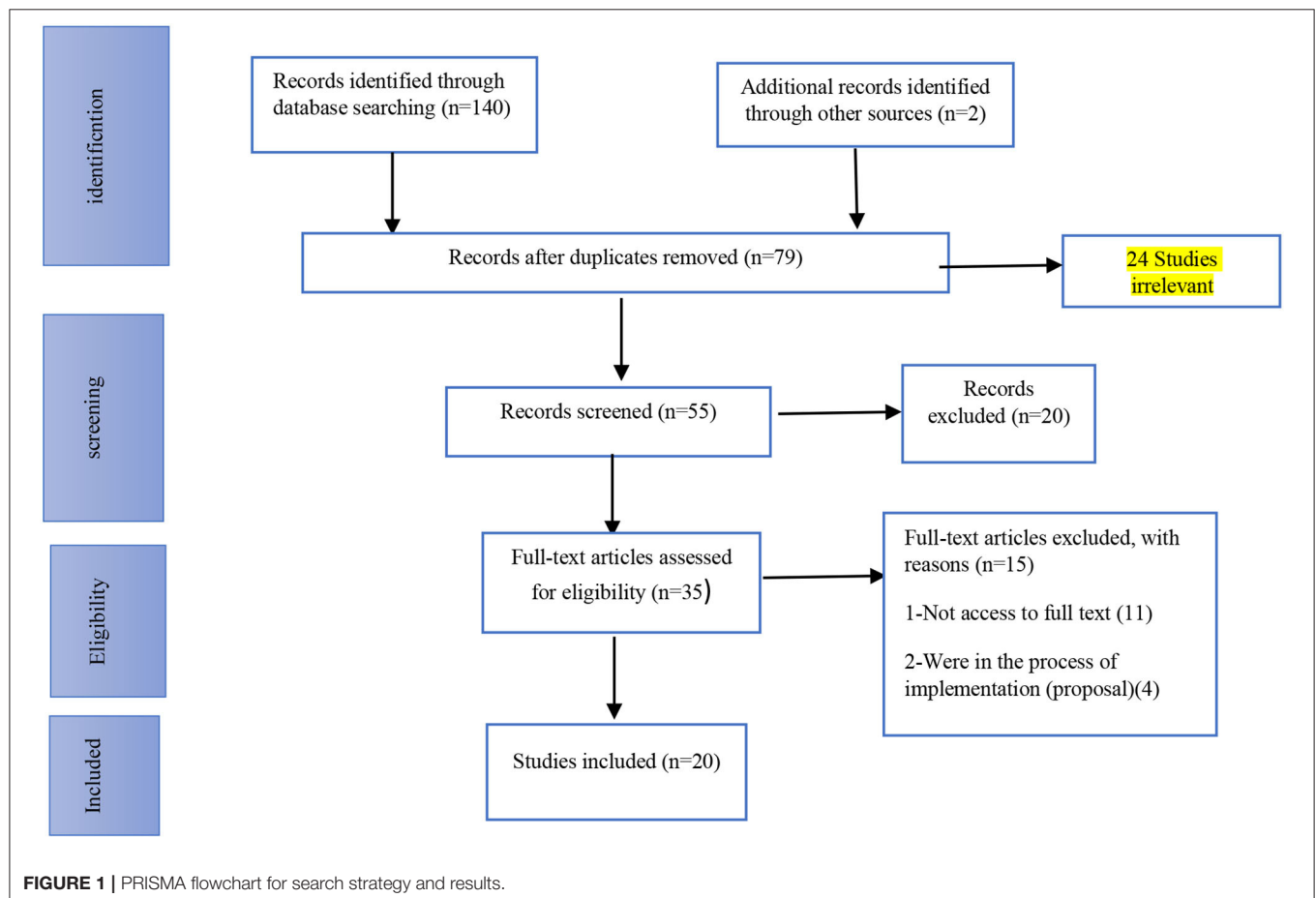
evaluated. In total, 35 studies were included in the selection phase, and 20 remained in the study (**Figure 1**). Twenty articles met the inclusion criteria and were included in the final analysis. The details are displayed in **Table 2**.

The 20 remaining studies were published between 2010 and 2021. Five of them were review studies (systematic, meta-synthesis and integrated reviews). Seven reviews were of qualitative type (grounded and content analysis), seven reviews

TABLE 2 | A summary of the critical review of previous Iranian and foreign studies.

No	Authors (Year)	Title	Target group, sample size	Important results and interpretations
1	Laurant et al. (36)	Replacing physicians with nurses in PHC	Systematic review $N = 18$	The care provided by nurses has similar or better health outcomes than the care provided by physicians. Findings showed that primary health care (PHC) directed by nurses reduced mortality in certain groups of patients. There was an increase in patients' satisfaction and quality of life compared to when care was provided by physicians. Nursing consultations were longer and the number of patient's follow-ups was higher with nurses than with physicians. Therefore, since the cost of hiring a nurse is lower than that of a physician, health nurses can be employed instead of physicians.
2	WHO (6)	Study on the status of community health nursing in 22 countries	Cross-sectional study $N = 432$	In African and Southeast Asian countries working condition for community health nurses was poor and unsafe, and lacked resources and the opportunities for the development and the enhancement of the profession. However, in the United States, health care institutes were well-equipped for community health nurses. The findings of the study showed that less than 10% of community health nurses fulfilled the roles regarding health promotion, disease prevention, and client consultation. Therefore, according to this fact, community health nurses less frequently participate in community-based activities
3	Kemppainen et al. (13)	Nurses' role in health promotion practice	Integrated review study $N = 40$	The vague and unclear concept of *health promotion* for nurses, their lack of skills and knowledge of performing health promotion activities, the lack of resources, and insufficient time are important challenges in the field of health promotion. Organizational culture is a key factor in nurses' activities in the field of health promotion. Managers in the organization should value health promotion activities, play a supportive role for nurses in this regard, provide sufficient resources and facilities to nurses for their practice, and continuously train nurses according to the health needs of the community
4	Heydari et al. (18)	The position of community-based nursing in Iran	Qualitative content analysis study $N = 20$	Important challenges in providing community-based nursing include not defining clear job descriptions for community health nurses, the lack of an effective management system to plan the use of community nursing services, the lack of a position for community health nurses in the family physician team, and people's distrust of nurses' capability to provide prevention services. One solution to overcome the challenges is creating an appropriate infrastructure (creating job opportunities, changing policymakers' attitude toward community-based nursing, and preparing the community to accept community-based nursing services)
5	Heidary et al. (2)	The position of nursing in the health service delivery system in Iran	Traditional review study	The main challenge is not being aware of nurses' capabilities in the field of health promotion and prevention, resulting in the very low activity of nurses in health care centers, which is why most nurses work in hospitals (the second level of prevention). Services provision settings for nurses are very limited in the community. Therefore, making reforms in the Iranian health system is necessary. Nursing officials should also work to promote and explain the position of nurses in the health system and prepare community health nursing students for the provision of services at the community level
6	Valaitis et al. (37)	The educational needs of community health nurses regarding the standards of community health nursing practice	Descriptive study ($N = 1344$)	Due to the increased cost of hospital-based care and the important role of community health nurses in health promotion and disease prevention, health system policymakers and decision makers should support this group by allocating sufficient resources to them in order to address their educational needs. Community health nursing instructors and teachers should also adjust their educational content to the needs of students and develop a continuing improvement educational program for community health nursing graduates
7	Philibin et al. (12)	Public health nurse's role in changing the community	Qualitative content analysis ($N = 25$)	The scope of public health nurses' practice is so wide that it includes comprehensive clinical care. This variety of responsibilities often leads to an increased workload and will hinder their practice in the field of health promotion. Therefore, it is recommended to redefine the roles of public health nurses with emphasis on its specialization, because public health nurses play a valuable role in providing community health services
8	Yuan et al. (9)	Community health nursing in China: status, challenges, and the strategies for its development	Descriptive study	The management of comprehensive health centers by physicians instead of community health nurses and the absence of community health nurses at high levels of policymaking hinders their effective practice. Low salary paid by community health centers is another challenge that has led to fewer nurses working in these centers than in hospitals. Therefore, it is necessary to acquaint health policymakers with the importance of community health nursing, to develop laws in support of these nurses, and to allocate sufficient funds to provide community health nursing services

(Continued)

TABLE 2 | Continued

No	Authors (Year)	Title	Target group, sample size	Important results and interpretations
9	Ildarabadi et al. (32)	Nursing students' perception of community health nursing education	Grand theory study ($N = 14$)	Nursing students' poor perception of community health nursing apprenticeship (a chance to rest and have fun, easy and simple content) and their treatment-oriented perspective lead to reduced productivity of community health nursing courses, and as a result, they don't have the required competency for practice at the community level after graduation. Therefore, it seems necessary that instructors correct the approach to community health nursing education
11	Schveitzer et al. (24)	Challenges of nursing in universal health coverage	Systematic review ($N = 30$: 29 qualitative studies, one quantitative study)	Nursing challenges for universal health coverage are related to education and preparation. Therefore, educating nurses is important for their effective performance in providing health services. The clear definition of nurses' roles in primary health care, interdisciplinary and multidisciplinary collaboration, community empowerment, technological advancements, professional communication with care seekers, and providing comprehensive and holistic care are needed to overcome the challenges
12	Mofrad et al. (38)	A comparative study of nursing role and position in the health system of Iran and the selected countries	Comparative study ($N = 18$ countries)	The role and the position of nurses in the Iranian health system have a much lower status compared to the selected countries, and despite the huge funds spent on nursing education at specialized levels, no position is defined for them in the health system promotion and most of them are recruited in hospitals. The preventive role of nurses in Iran is so insignificant that it can be said that such a role does not exist. Therefore, it is necessary for the policymakers to define the role and the position of nurses in the primary health care system
13	Kabayama et al. (14)	The role of community health nurses in long-term projects of preventive healthcare in Japan	Descriptive study	Community health nurses have the necessary knowledge and skills to work at the three levels of prevention. Community health nurses play a key role in providing care for communities with older population such as Japan In Japan, the demand for community health nursing services has increased due to its cost-effectiveness
14	Heravi et al. (19)	Nursing students' perception of apprenticeship in the community health nursing setting	Qualitative content analysis ($N = 19$)	The inadequacy of nursing instructors, the inefficiency of the executive management of apprenticeship, and the theory-practice gap are the challenges of community health nursing education. Therefore, the students' clinical education should be tailored to the needs of the community. These challenges should be considered to improve the quality of apprenticeship programs while planning them
15	Yazdani et al. (21)	An analysis of the healthcare system policymaking in Iran regarding professional nursing	Qualitative content analysis ($N = 6$)	Policymaking in Iranian health system is inappropriate in the field of nursing profession and factors such as the lack of mutual interaction among nursing sectors or other institutions of health care system, the unwillingness of these institutions to explore nursing, and nurses' lack of involvement in the policymaking in this area due to conflicts of interest. The development of disciplines parallel to nursing and the unclear scope of nursing practice in the field of health care services are among the other important challenges
16	Nkowane et al. (39)	Promoting the role of community health nurses for universal health coverage: a performance measurement of community health nursing in 13 countries	Cross-sectional study ($N = 13$ countries)	Community health nurses play an important role in universal health coverage. The performance of community health nurses requires the commitment of policymakers and managers to invest in the development of this profession. These countries had functional frameworks for the education, management, and provision of their services. These countries had appropriate supportive and motivational packages to retain community health nurses in health centers. Few community health nurses (15%) had received interdisciplinary training. Most community health nurses offered a variety of roles in health centers, for about half of which they had not received appropriate training
17	Shahshahani et al. (40)	A study on the status of health care delivery system in Iran	Triangulation study $N = 15$ stage 2 $N = 64$ stage 3	Considering the role of nursing in community health, it is recommended that appropriate planning be done by the health system policy makers in order to create a position in the health sector. The findings of this study showed that the biggest change in Iranian nursing is the provision of services and community-based activities
18	Gultekin (41)	The status quo of public health nursing in Turkey, the related issues and solutions	Descriptive study	Despite the fact that there are PhD courses in public health nursing in Turkey, the community health centers are run by midwives and few public health nurses work in these centers. Therefore, it is necessary to improve the personal rights of public health nurses, restore their occupational identity, and improve the conditions for providing comprehensive health care. The concept of community nursing and home care needs the support of policymakers, and the formulation and reform of laws

(Continued)

TABLE 2 | Continued

No	Authors (Year)	Title	Target group, sample size	Important results and interpretations
19	Heydari et al. (16)	The barriers against home care services in Iran	Qualitative content analysis (N = 17)	The cultural aspects of the Iranian community should be considered for developing a position for home care and the integration of nursing into the health system. Infrastructural problems such as the lack of executive protocols, the lack of insurance coverage and interdisciplinary issues should be solved. Treatment-based approaches, the prioritization of hospital care, and the single-dimensional management of the health system are among the other challenges in community-based nursing
20	Hossein Nejad et al. (31)	The requirements for developing community health nursing position in the PHC system in Iran	Qualitative content analysis (N = 24)	One of the requirements for creating a position for community health nursing in the primary health care system of Iran is focusing on the dimensions *creating a transparent framework for community health nursing practice*, *promoting community health nursing education and training for practice in primary health care system and community settings*, *seeking support*, *strengthening cooperation and engagement among the key stakeholders of the primary health care system*, *changing policies and the structure of the health system*, and *focusing on the deficiencies of the health system*. These policies, if properly and correctly implemented in the socio-cultural context and background of the community based on the primary health care system and in line with the efforts and policies of the health system, can help policymakers pay more attention to the challenges that hinder community health nursing practice in the health system

were cross-sectional descriptive, and one was a comparative study. Eighteen reviews were published in English and two were published in Farsi. The majority of the reviews investigated the position and the role of community health nursing in the health service delivery system and its challenges. About 40% of the reviews are related to the studies on the situation of community health nursing and the barriers against its provision in Iran. Two reviews have studied community health nursing education in Iran, and seven reviews proposed strategies to solve the challenges of community health nursing.

Findings

By analyzing the reviews, six themes emerged in the field of community health nursing challenges, and six other themes concerned the strategies to overcome the challenges. The details are displayed in **Table 3**.

The Challenges of Community Health Nursing in Iran
There are several challenges regarding community health nursing in Iran, which have been addressed in previous studies (**Figure 2**)

Challenges of Community Health Nursing Education
Several challenges were mentioned in the literature in regard with the education, which were divided into the three areas *input*, *process,* and *output*.

Input. Students' poor understanding of community health nursing lessons, considering the community health nursing apprenticeship as futile, and, in some cases, even as a chance to rest, as well as their poor motivation for active participation were mentioned as important challenges (32). Moreover, nursing students' treatment-based and disease-based perspective and their poor community-based and holistic perspective is another challenge in this area (1, 2).

Another challenge in this area is the insufficient skills and experience of nursing educators in the field of community-based educational planning, their inadequacy in conducting community health apprenticeship programs and the related evaluations, and ineffectiveness of community health apprenticeship (19, 42). In another study, the low quality of community health nursing education, the use of traditional methods, reviewing theoretical topics during apprenticeship, and not implementing appropriate educational models were mentioned as challenges (1, 19). Other studies have shown that the educational system of medical universities is not adjusted to PHC and the educational content is not tailored to the needs. Therefore, the university graduates do not have the required skills to deal with problems and academic education courses should be promoted and based on PHC (22, 47).

The Process. The poor presence of community-based care in the nursing education and focusing on hospital care have been referred to as one of the most important challenges according to several studies. Nursing education in Iran is more focused on clinical education. Most nursing schools train their students to play the traditional nursing role, while community needs the training of nurses according to holistic perspectives (1, 16, 19, 40). Limited community health credits and the hours of apprenticeship in health centers will lead to poor productivity of apprenticeship programs (2, 31). The theory-practice gap, i.e., the inapplicability of some health theory content in the apprenticeship settings, and the lack of community-based education standards in nursing were mentioned as other challenges in this field (1, 19).

Output. Recruiting nurses only in clinical settings such as hospitals and the absence of a particular and appropriate professional position for nursing and community health nursing

TABLE 3 | The challenges of community health nursing and the
identified solutions.

Authors	Challenges
	Community health nursing training
Karimi et al. (1), Ildarabadi et al. (32), Heravi et al. (19), Heydari et al. (16), Shahshahani et al. (40), Hosseinnejad et al. (31), Cheraghi et al. (42)	1. Input 2. Process 3. Output
	Community health nursing practice
Yazdani et al. (21), Hosseinnejad et al. (31), Heydari et al. (16), Heydari et al. (18)	Not defining a position for community health nursing service delivery Recruiting community health nurses only at hospitals and treatment settings No clear job descriptions for community health nurses
	Policymaking in the field of community health nursing
Hosseinnejad et al. (31), Yazdani et al. (21)	Lack of interaction between nursing managers and the policymakers of the Ministry of Health Not involving nurses in policymaking regarding their discipline Policymaking in community health nursing
Heidary et al. (2), Heydari et al. (18), Shahshahani et al. (40)	Managerial measures Not being acquainted with community health nursing profession
	Infrastructure
Hosseinnejad et al. (31), Heydari et al. (16), Barasteh et al. (29), Heydari et al. (16)	Insurance coverage and funding Executive protocols Interdisciplinary cooperation
	Culture
Heydari et al. (16), Heydari et al. (18)	Public distrust of and negative attitudes toward the capabilities of non-physician experts
	Solutions
	Community health nursing training
Heravi et al. (19), Alizadeh et al. (43), Gimenes et al. (44), Karimi et al. (1), WHO (6), Barasteh et al. (29), Cheraghi et al. (42), Ildarabadi et al. (34)	Holding courses on the empowerment of community health instructors Offering specialty community health nursing programs instead of routine and usual clinical care Reforming nursing curriculum focusing on community-based training Changing educational approaches in community health apprenticeship
	Community health nursing practice
Karimi et al. (1), Barasteh et al. (29), Mofrad et al. (38), Yuan et al. (9), WHO (6), Heydari et al. (16)	Revising and reforming the community health nurses' recruitment process Developing an organizational title for the recruitment of health nurses at the community level Formulating the job descriptions and the roles of community health nurses
	Policymaking
WHO (6), Heidary et al. (2)	Involving community health nurses in the issues related to national health Formulating laws in support of community health nurses
	Management
Ranjbar et al. (30), Yazdani et al. (21), Yuan et al. (9), Oros et al. (45), WHO (6), Jamshidi et al. (46)	Supporting community health nurses for the establishment of community health clinic Using motivational strategies for attracting community health nurses Explaining the concept of the community health nurse and its capabilities
	Infrastructures
Oros et al. (45), Heydari et al. (16), WHO (6), Jamshidi et al. (46)	The insurance coverage of community-based care Strengthening inter-sectoral and interdisciplinary cooperation

(Continued)

TABLE 3 | Continued

Authors	Challenges
	Culture
Heydari et al. (16), Heydari et al. (18)	Introducing the community health nurses' role and promoting public awareness of it
	Research
Kemppainen et al. (13), Yuan et al. (9), Heidary et al. (2)	Investigating the effectiveness of health nursing in the public health promotion

graduates in health centers has prevented nursing graduates from acquiring the necessary skills to provide health care (31, 42).

Practical Challenges of Community Health Nursing

One of the most important challenges in this field is not defining positions for the provision of nursing services in the community and various settings of the health system. Therefore, in hospitals, which are considered as the main position of nurses, appropriate roles are not defined for them with the aim of health promotion (21). Another challenge is hiring nurses and community health nurses in medical settings and hospitals. Nursing care in Iran focuses on the provision of care at the secondary level of prevention; therefore, the preventive role of nurses is overshadowed and nurses are not involved in health care homes and comprehensive health centers, which is the first level of people's contact with the health care system (16, 31, 40). The lack of adequate and proper health care in remote and rural areas is one of the biggest national concerns, and most of the health care workers in rural and remote areas are Behvarzes (rural health workers) and practical nurses, while no job opportunities exist for community-based nursing postgraduates in comprehensive health centers, prevention units, and health care homes (2). The lack of clear job descriptions for community health nurses and community-based nursing in the country is another challenge, as community health nursing is only a field for study, not suited for practice (18). Another important challenge will be the inadequate professional development of nursing compatible with the needs of community, the lack of competent staff in the field of community-based nursing, and the lack of nursing promotion in accordance with the pattern of diseases in the country (29).

One of the important areas of community health nursing is performing home visits and the provision of care and counseling in the home environment. A challenge that community health nurses face in this regard is the problems with ensuring their safety (16).

Policymaking Challenges in Community Health Nursing

The lack of mutual interaction between nursing and other institutions of the health system and nurses' lack of involvement in policymaking regarding their own field of study has resulted in neglecting the role and the position of nurses in the health system. On the other hand, health policy makers have not taken the nursing profession seriously because physicians are dominant in the health system. In other words, the nurse's role and position in the field of prevention and community-based services has been

FIGURE 2 | Community health nursing challenges in Iran.
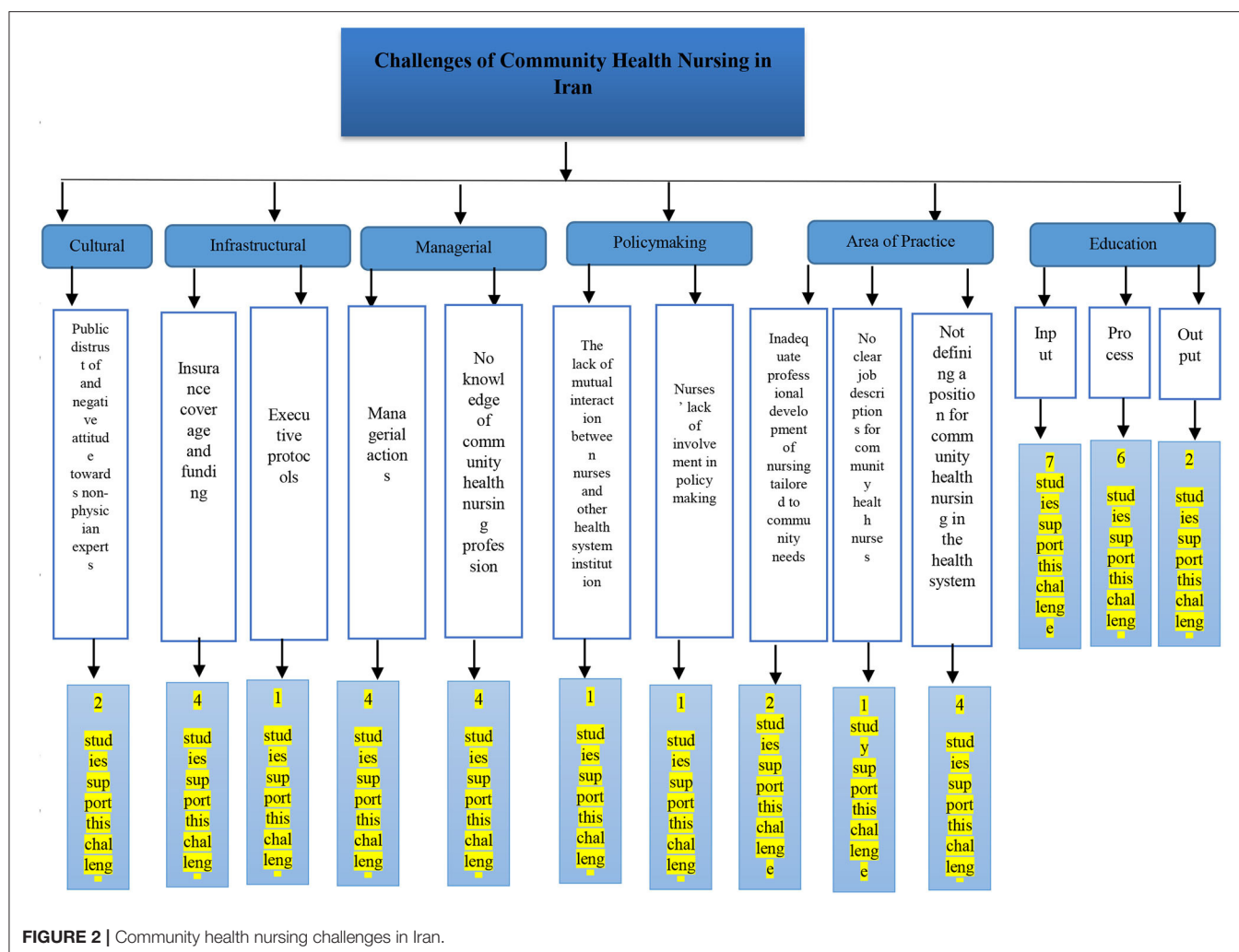
ignored. The chaos and the disorder in the health system, as another challenge, has prevented the fulfillment of one's actual role (21). On the other hand, the absence of interaction between nursing managers and the policymakers of the Ministry of Health to identify community health nurses' potentials is another challenge (31).

Managerial Challenges in the Field of Community Health Nursing

In the field of management, several challenges have been mentioned in the articles, which were divided into two areas: *managerial actions*, and *the lack of knowledge of the community health nursing profession.*

Managerial Actions. The lack of an effective management system for the use of community health nursing services has been mentioned as one of the most important challenges, as health managers have to make appropriate strategic plans (18). Another important challenge mentioned in the studies is the existence of specialty and subspecialty service providers in the health system, which has hindered the establishment and the development of

health promotion centers; in other words, community-based care has no place in the Iranian health system (16). The managers' not using motivational mechanisms to encourage community health nurses to work in health centers is referred to as another challenge. One of the major motivating factors is the allocation of salaries and financial benefits, but since the health personnel's salaries are lower than those of the staff in treatment sectors, community health nurses are less motivated to work in the field of health (2, 31).

The Lack of Knowledge of Community Health Nursing Profession. One of the important challenges is nursing institutions' lack of knowledge of nursing and its specialty disciplines (40). The health managers' lack of knowledge of the capabilities of nursing and community health nursing has resulted in their limited presence in community health service centers and the concept of community health nurse's role (2, 31, 40). In addition, Iranian health managers have not considered a position for community health nurses in the family physician team, because these authorities do not have any knowledge of the community health nursing profession (18).

Infrastructural Challenges

In regard with of infrastructure, several challenges were pointed to in the articles, which were divided into three areas: *insurance coverage and funding, executive protocols*, and *interdisciplinary cooperation*.

Insurance Coverage and Funding. Another challenge is the high cost of health service provision in the community in the form of home visits and the fact that they are not paid by insurance. Allocating less funds for providing community-based care than for treatment care and hospitalization is another challenge in the Iranian health system (16, 17, 31, 33).

Executive Protocols. The absence of clear guidelines for making assessments, classifying patients and care seekers, wages and salaries, allocating funds and determining personnel adequacy and competency in the community-based care and home care system is another important challenge in this regard (16).

Interdisciplinary Cooperation. There is no interdisciplinary cooperation and coordination among different sectors of community such as health centers, municipalities, and the police to provide community-based care by community health nurses (16). While the desirable future of the community health nursing profession requires cooperation and communication with other institutions such as the Welfare Organization, the municipality, and the Broadcasting Corporation (29). On the other hand, Iranian health system is governed through unionism and tribalism. Therefore, as long as there is unionism, no interdisciplinary cooperation and partnership should be expected (31).

Cultural Challenges

Public distrust of and negative attitude toward the capabilities of non-physician experts in providing prevention and health services is another challenge in Iran (2, 16).

Solutions

In previous studies, several strategies were mentioned for each group of community health nursing challenges.

Appropriate Solutions to the Challenges of Community Health Nursing Education

Input. In order to solve the challenges in this area, the following strategies can be used:

1. A solution to instructors' challenges: one strategy is to hold training courses for community health instructors so that they can provide and train quality nursing services outside the hospital. It is also possible to provide information on new educational strategies, novel learning opportunities in the field of community health, new tools, and new methods of student assessment to the community health nursing instructors in workshops. In addition, qualified instructors should be hired to teach community health, and short-term training programs should be developed and prepared in the field of geriatric nursing, school nursing, occupational nursing, community-based rehabilitation, and behavioral disease counseling for senior community health nursing professionals in order

to promote nurses' position and role in the educational, treatment, and health care teams (1, 2, 19, 43, 44).

2. A solution to students' challenges: the strategy is to hold pre-teaching workshops in various fields of community health with the aim of preparing students to share their apprenticeship goals and motivate them. Furthermore, to train nursing students for community health nursing discipline, participatory processes with key stakeholders such as health centers and deputies, regional hospitals, clinics and schools as well as specialty nursing programs should be used to empower nurses, instead of providing conventional and routine clinical trainings (1, 6, 16).

Process. Modifying nursing curriculums with the aim of focusing on community-based education, developing evidence-based curriculums based on the health needs of different regions of the country, and considering community health nursing practice is an effective strategy (1, 2, 29). Measures can be taken to overcome challenges in this area through changing teaching methods in apprenticeships (considering working with the community and family instead of the individual) and using nursing theories, including Betty Neuman's theory in community health education, the main purpose of which is comprehensive and continuous patient care and, accordingly, the actual position of nurses in care is all the three levels of prevention. We can take steps to address the challenges in this area (1, 42). Using multiple approaches, and a combination of different methods in community health nursing apprenticeships has been effective in increasing nursing students' competence. Training courses in the field of community-based visits (home, schools, factories, and stores) had a positive effect on changing students' attitudes toward community services (34).

Appropriate Solutions to the Practical Challenges of Community Health Nursing

This group of challenges can be addressed by reviewing and reforming the process of hiring community health nurses and creating an organizational title for hiring community health nurses in schools, factories, prisons, and comprehensive health centers (1). In other words, this challenge can be overcome by shifting the health care delivery setting to the community, integrating nursing services into primary health care and focusing on health promotion and disease management (29, 38). In addition, reviewing the educational needs of community health nursing graduates to provide ongoing responses to public health needs, especially plans to improve the skills and the abilities of nurses, is one of the effective solutions to this group of challenges (46). At large scale, nursing managers should formulate the job descriptions, roles, and responsibilities of community health nurses (6, 9, 16).

Solutions to Policymaking Challenges in Community Health Nursing

This challenge is possible to be solved by involving community health nurses, as professionals in this field, in health-related issues at large scale. Policymakers should also publicize laws and policies in support of community health nurses and develop

guidelines that align community health nurses' roles with their skills and areas of practice (1, 2, 6, 26). It is suggested that legislators prioritize accountability principles based on community, justice, and accessibility. In addition, policymakers need to develop a strategy to reform policies in order to lay the ground for the development of nursing at the community level (33).

Solutions to Managerial Challenges in Community Health Nursing

Health and treatment managers should support community health nurses in establishing community health clinics (1, 6, 21, 30). Nursing managers should also take action to set up home visit centers using a health promotion approach with the help of community health nurses (33, 46). Nursing managers should take the necessary measures to explain and promote the concept of *community health nurse* and its capabilities (46). Furthermore, health system managers should use motivational strategies to attract and retain competent community health nurses (6, 9, 45).

Solutions to Infrastructural Challenges in Community Health Nursing

Nursing managers should provide appropriate guidelines and instructions for community-based care and its management and the insurance coverage of home and community based care and services, as is done in developed countries, which results in more people seeking this type of service from community health nurses (6, 9, 16, 45). Necessary measures should be taken to increase inter-sectoral cooperation between the nursing profession and different fields of community in order to progress, address global health objectives, and strengthen interdisciplinary cooperation (46).

Solutions to the Cultural Challenges of Community Health Nursing

Strategies that are effective to address this challenge include informing the community and raising public awareness of the significance and the role of nurses in providing and offering community-based services through social media, as well as developing comprehensive supportive programs in collaboration with the Nursing Deputy of the Ministry of Health, Iranian Nursing Organization, and the National Broadcasting Corporation in order to raise public awareness and understanding of community health nursing (16, 18). Moreover, some studies have proposed a research approach to address the challenges in various fields of community health nursing. Some examples are conducting research to evaluate the effectiveness of community health nursing approach and determine the position of nursing in the health care system, or doing more research on the services provided by community health nurses to make the other members of the health team acquainted with their activities (2, 9, 13).

DISCUSSION

The aim of this study was to investigate the challenges of community health nursing in Iran and the related solutions in an integrated manner. According to this study, the main challenges included the challenges of community health nursing education, practical challenges in community health nursing, policy-making challenges in community health nursing, managerial challenges in community health nursing, and infrastructural and cultural challenges.

It was discovered that the factors related to community health nursing education are among the challenges. Since health care delivery to people has shifted from hospitals to community centers, nursing students should be educated through community-based approaches. The results of a study on the experiences of nursing instructors showed that the practical training of students in the field of community health is not compatible with the needs of community and education is not community-oriented (48). According to other studies, although one of the goals of community health nursing education is community-based education, it is currently forgotten and ignored (1, 49). The results of the study by Oros focused on education through community-based care models instead of using traditional health models (45). The results of a systematic review study also showed the impact of the effective training and the preparation of nurses in the practical fields of community health to overcome the challenges of community health nursing (24). In their study, Jarrín et al. (50) stated that launching a community health nursing education program in the form of lectures in the first months of university, introducing textbooks, and performing simulations regarding community and home care will significantly affect their attitudes toward and beliefs about community-based nursing because traditional curriculums has resulted in the students' considering community activities and home care unimportant.

The approach through which nurses have been educated during the 20th century is not tailored to the health care needs of the health system in the 21st century. Therefore, nursing educators and planners should constantly review the content of community health nursing education based on the needs assessment of community health students and graduates and according to the needs of the community (37, 44). The study by the World Health Organization also considered the lack of educational standards for community health nursing as a challenge and referred to the need to develop programs in accordance with the educational needs of community health nurses (6). Kemppainen et al. (13) showed that continuing education in accordance with the needs of nurses is effective in their performance in the field of health promotion. Another challenge in this area is the community health nursing instructors' inadequate skills and experiences in providing effective education. In another study, Khorasani reported that the training and nursing courses for nursing students in the field of community health nursing are more focused on filling out care seekers' medical records and collecting health statistics and reports, which are usually done by midwifery or primary health technicians. However, it is less focused on issues such as establishing close relationships with the community and especially families in community health apprenticeship and pays more attention to reviewing theoretical content and superficial visits (51). In other studies, students considered community

health apprenticeship futile and useless and believed that there is a relative relationship between theoretical education and the practical field of community health nursing (52, 53).

Challenges related to the field of community health nursing practice are also very important. One of the challenges in this dimension is the lack of competent workforce in the field of community-based care. This finding is in line with the study of Kemppainen et al. (13). One of the reasons behind this is the lack of job opportunities for them to acquire the necessary skills and the lack of retraining courses, while in developed countries like Denmark, nursing graduates are able to make assessments and planning, perform prevention, treat all patients and provide community-based care (54). Another challenge in the practical field of community health nursing in Iran is the lack of a clear job description for community health nurses. In the study by the World Health Organization, disagreement on community health nursing performance was mentioned as one of the important challenges (6). In their study, Kemppainen et al. (13) considered the lack of clarity in the nurses' job descriptions and activities in the field of health promotion as a barrier. In another systematic review study, the lack of a clear definition of the nurses' role in PHC has been mentioned as an important challenge in achieving universal health coverage (24).

Another challenge lies in the field of community health nursing policymaking. What was mentioned in the studies shows the impact of the structure and policies of the health system on not creating an appropriate position for community health nurses in the field of community-based and community-oriented health services. Many countries have given nurses the opportunity to provide primary health care to develop the quantity and the quality of health care in their communities. At present, in the Iranian health system, changes are taking place without considering the needs of care seekers and the costs of health care increase with the rise in the elderly population and the higher percentage of chronic diseases in the community (23). A study conducted in Oman also showed that community health nursing is not considered as much important as hospital-based nursing by the policymakers (55). In the study by Yuan, the lack of community health nurses' participation in health policymaking and planning is one of the major challenges in providing community health nursing services (9). According to the WHO, one of the most important challenges is the lack of public commitment and the policymakers' incapability to execute regional and global policies for community health nurses (6).

Another important challenge is management. One of the challenges in this area is the lack of motivational mechanisms for encouraging community health nurses. In a WHO study, the environment and the non-supportive conditions of community health nurses are stated as challenges and the use of motivational strategies to attract and retain competent community health nurses is regarded as a solution (6). The study of Kemppainen et al. (13) showed that in the organizational culture, the presence of health managers who support nurses in providing health services is an effective factor in nurses' health promotion practice. Another challenge in this area is the health system managers' lack of knowledge of community health nursing, which is consistent with the study conducted by WHO (6). Therefore, considering

the emergence of global health threats, it seems necessary to clarify the concept of community health nursing.

Infrastructural challenges are another type of challenge according to this study. Currently, the focus of the health system on disease-oriented approaches rather than prevention is an important reason for the huge amount of money spent in the treatment sector, and causes issues in the allocation of resources to the community health nurses in the field of health promotion. The results of the study by Yuan also regarded the lack of sufficient funding for the provision of community-based nursing services as a significant challenge (9). Moreover, an Omani study reported community health nurses' limited access to equipment and lower funding for implementing the program (55), which is in line with the study of Kemppainen et al. (13). Other studies in other countries have shown that the amount of nurse salaries at the community level and in the society is lower than in medical centers, and these underpaid nurses who provide services at the community level are pushed to work in the treatment sector (56, 57). Another challenge in this area is poor interdisciplinary cooperation. The World Health Organization also considers poor interdisciplinary cooperation with other professions as one of the major challenges of community health nursing (6). Investing in interdisciplinary teamwork is considered as a way to overcome the challenges of nursing in providing primary health care (24).

Cultural issues are regarded as another important challenge. People's distrust of non-physician experts' capabilities is a challenge in this area. A Chinese study also showed the lack of public trust in community health nursing services (9). However, according to the study by the WHO, non-physician staff are also able to provide similar care to patients (58). The findings of another systematic review study aimed at investigating the impact of replacing physicians with nurses in PHC in the care procedure, patient outcomes and cost analysis showed that the care provided by nurses had similar or better health outcomes compared to the care provided by physicians (36). According to the WHO, if the health system wants to address the health needs of the community, it must use nurses and midwives (59). The existence of a communication channel for community health nurses is essential to raise public awareness through the media (47). The study of Heydari et al. (18) also emphasized on preparing the community and raising public awareness in order for them to receive community-oriented nursing services. Therefore, it is necessary to explain the important role of nurses in providing health services to the public.

Considering that all the challenges mentioned in these studies can also be applied to Iranian community health nursing in Iran, it is possible to take an important step toward solving these challenges in the country's health system by implementing the proposed strategies.

Limitations

This integrated review has several limitations. The authors' knowledge of the challenges of community health nursing and the solutions is limited to the data documented in the articles. Therefore, if the challenges are not fully described or reported by the authors, they will not be reflected in the results. Only

credible articles in English and Farsi were reviewed; as a result, the articles and the related data from initial research and gray literature published in other languages may have been omitted. The authors did not seek to evaluate the quality of the studies and did not compare them with similar ones. However, our integrated review is an attempt to combine the results of the studies and the research approaches. Finally, these results are more related to community health nursing challenges in Iran. Future research should address the challenges of community health nursing at a global level.

CONCLUSION

Considering the results of the present study, it can be concluded that the challenges of community health nursing in Iran, including the lack of an appropriate position for community health nursing, nursing education ignoring community-oriented care, and inappropriate infrastructure are inter-wound issues dependent on each other that affect community health nursing practice. Therefore, in order to solve these challenges, it is suggested that the policy makers and the managers of the health system modify the structure of the health system so as to move from a treatment-oriented approach toward a community-oriented one, develop supportive laws and job descriptions for community health nurses, and create an organizational chart for community health nurses at the community level. It is also recommended to use motivational strategies to attract community health nurses and support them in establishing community health clinics, and to cover community-based services and care under insurance. Moreover, nursing education administrators should modify nursing students' curriculum with the aim of focusing on community-based education. In addition,

in order to solve the challenges in this field, community health nursing leaders should try to increase cross-sectoral and inter-professional cooperation, promote the profession, and make the capabilities of community health nurses recognized by other professions and the public.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

The data analysis and manuscript were prepared by AH with support from SJ, MR. All authors critically reviewed and contributed to the manuscript and approved the final version.

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Population-Level Interventions Targeting Risk Factors for Hypertension and Diabetes in Rwanda: A Situational Analysis

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Background: Eighty percent (80%) of global Non-Communicable Diseases attributed deaths occur in low- and middle-income countries (LMIC) with hypertension and diabetes being key contributors. The overall prevalence of hypertension was 15.3% the national prevalence of diabetes in rural and urban was 7.5 and 9.7%, respectively among 15–64 years. Hypertension represents a leading cause of death (43%) among hospitalized patients at the University teaching hospital of Kigali. This study aimed to identify ongoing population-level interventions targeting risk factors for diabetes and hypertension and to explore perceived barriers and facilitators for their implementation in Rwanda.

Methods: This situational analysis comprised a desk review, key informant interviews, and stakeholders' consultation. Ongoing population-level interventions were identified through searches of government websites, complemented by one-on-one consultations with 60 individuals nominated by their respective organizations involved with prevention efforts. Semi-structured interviews with purposively selected key informants sought to identify perceived barriers and facilitators for the implementation of population-level interventions. A consultative workshop with stakeholders was organized to validate and consolidate the findings.

Results: We identified a range of policies in the areas of food and nutrition, physical activity promotion, and tobacco control. Supporting program and environment interventions were mainly awareness campaigns to improve knowledge, attitudes, and practices toward healthy eating, physical activity, and alcohol and tobacco use reduction, healthy food production, physical activity infrastructure, smoke-free areas, limits on tobacco production and bans on non-standardized alcohol production. Perceived barriers included limited stakeholder involvement, misbeliefs about ongoing interventions, insufficient funding, inconsistency in intervention implementation, weak policy enforcement, and conflicts between commercial and public health interests. Perceived facilitators were strengthened multi-sectoral collaboration and involvement

in ongoing interventions, enhanced community awareness of ongoing interventions, special attention paid to the elderly, and increased funds for population-level interventions and policy enforcement.

Conclusion: There are many ongoing population-level interventions in Rwanda targeting risk factors for diabetes and hypertension. Identified gaps, perceived barriers, and facilitators provide a useful starting point for strengthening efforts to address the significant burden of disease attributable to diabetes and hypertension.

INTRODUCTION

Non-communicable diseases (NCDs) claim about 41 million deaths each year, equivalent to 71% of global deaths (1), of which 80% is in low- and middle-income countries (LMIC).(2, 3). Both hypertension and diabetes are major contributors to NCD deaths (4). Hypertension is a key risk factor for cardiovascular diseases (CVDs) (5). Globally, an estimated 1.13 billion people have hypertension, two-thirds are from low-middle-income countries (LMICs) (6). More than 1.6 million deaths in 2015 were due to diabetes, while 422 million adults live with diabetes (5).

People with diabetes are at high risk of CVDs (7, 8). The number of people living with diabetes in Sub-Saharan Africa (SSA) was estimated at 12.1 million people in 2010; this number is expected to rise to 23.9 million by 2030 (9, 10) and to 47.1 million by 2045 (11), with the onset at a younger age in LMICs (12, 13). In Rwanda, the national prevalence of diabetes in rural and urban was 7.5 and 9.7%, respectively among 15–64 years (14) whereas the overall prevalence of hypertension was 15.3% (16.4% for males and 14.4% for females) (15).Hypertension was a leading cause of death (43%) among hospitalized patients at the University teaching hospital of Kigali in Rwanda (16). The latest published NCDs risk factors survey revealed that 19% of men and 7% of women were tobacco smokers, 30% of men and 17% of women had binged on alcohol in the past 30 days and 99% of participants consumed <5 servings of fruit and/or vegetables per day (17). The majority of NCDs can be prevented through various preventive measures including policies and various interventions (18). The sixty-sixth World Health Assembly (WHA) held in 2013 called for a 25% reduction in NCD deaths by 2025 (19). A study done in China, India, and Mexico showed that community-based interventions for health are scalable to the population-level, affordable, and effective in controlling risk factors for NCDs in LMICs (20). Beyond the WHA target, NCDs Synergies network and the Rwanda Ministry of Health (MoH) have set the target to reduce 80% of NCD-related deaths among people under 40 years of age by 2020, through various population-level interventions and integrated health service delivery platforms (21). This ambition was believed to be achieved through leveraging the existing investments. Rwanda went ahead to implement some of the population-level interventions. Population-level interventions are made up of supporting environment (activities influencing the creation of environment in which healthy choices are the easier option for the population; example: playgrounds for physical activity), supporting policies (fiscal, legislative, and regulatory measures that foster and promote healthy choices; example: tobacco control policies) and programs (activities implemented at all levels to promote healthy choices of the community; example: salt intake reduction awareness campaign) (22). It is not exactly known which and to what extent population-level interventions are being implemented in Rwanda. This study aimed to provide a comprehensive overview of the currently implemented population-level interventions targeting risk factors for diabetes and hypertension, as well as to explore perceived barriers and facilitators affecting implementation using multiple approaches.

METHODS

Study Design, Sampling and Data Collection

This situational analysis was conducted in parallel across three African countries (Rwanda, Malawi, and South Africa) using a standardized but locally adapted protocol. In Rwanda, which is described in this study, the situational analysis was conducted from February to September 2019. It comprised a desk review, semi-structured interviews with purposively selected key informants, and a one-day consultative workshop.

The desk review consisted of two phases: an online search of policy documents and consultations with selected stakeholders. In the first phase, we searched the government website (https://www.gov.rw/) to obtain relevant policy documents from various ministries and agencies involved in population-level interventions targeting risk factors for diabetes and hypertension. Additional documents were requested directly from key stakeholders, specifically from Rwanda MoH and the Rwanda Biomedical Center (RBC). Retrieved published and gray literature were searched using terms such as diabetes mellitus or hypertension, population, prevention, and Rwanda plus a risk factor of interest. A document was eligible for in-depth review if it contained at least one of the information regarding the design, implementation or evaluation of population-level interventions to address NCD risk factors in Rwanda. An Excel

spreadsheet was designed to extract relevant information on what are the implemented population-level interventions and the extent of their implementation (target population, coverage and the evaluation status) from all eligible documents. In the second phase of the desk review, we used information from the first phase to map several stakeholders involved in implementation of population level interventions. The mapping for stakeholders started with purposive reaching out to relevant personnel from the Ministries of Health and other governmental or non-governmental agencies already known to be actively involved in implementation of population level interventions and then using snow-balling method, 40 various key stakeholders (governmental or non-governmental) were mapped. Forty mapped institutions and organizations through a written letter, they were introduced to the current study and requested to nominate individuals who are knowledgeable in implementation of population level interventions of interest to talk to in a one-on-one (face-to-face) consultation, these were mainly people who are current working in NCDs unit in health sector, NCDs focal person or work closely with NCD technical working group for non-health sector. As a result, 60 individuals across different managerial and technical levels of these organizations were nominated and voluntary agreed to participate in the study. In some institutions, more than one person agreed to participate in our study. After obtaining their signed consent to participate in the study, a trained data collector used a designed data extraction sheet to collect their insights on ongoing population-level interventions in Rwanda. The information identified in this manner complemented data from the online search to provide a comprehensive overview of population-level interventions targeting risk factors for diabetes and hypertension implemented in Rwanda.

Semi-structured key informant interviews were conducted with a sub-set of key informants from across concerned institutions. Active involvement with ongoing population-level interventions as well as the diversity of the interviewees (i.e., policymakers, implementing agencies, and non-governmental organizations) and managerial as well as technical knowledge were considered in selecting key informants. We targeted NCDs focal people, heads of NCDs unit and members of national NCD technical working group because they fulfilled all these above mentioned criteria. Ten participants were chosen for pragmatic reasons for key informants interview. We used a structured interview guide consisting of open-ended questions designed and pilot- tested for this study. Participants were asked of their view on what was hindering (perceived barriers) and facilitates (perceived facilitators) the implementation of population-level interventions. Interviews with participants were undertaken by trained interviewers (DJ, UI, GJB, NJ, and BC), took place at the participants' workplace and lasted for 20 to 30 min. Both recording and note taking were done to accurately capture the contents of the interviews. Following a preliminary analysis of the data, a one-day consultative workshop to validate and consolidate findings was held with at least one participant representing each of the institutions that participated in this study.

Data Analysis

Desk review data (website searches and one-on-one consultations) and qualitative data (key informant interviews) were analyzed separately because they answered different objectives. For desk review, both data from website searches and one-on-one consultations were compiled in a spreadsheet. Two researchers (JPN&DKT) independently classified interventions as policies, programs, and supporting environment interventions per each of the four main NCD risk factors (unhealthy diet, physical inactivity, tobacco use, and harmful use of alcohol). They (researchers) compared their findings and resolved any disagreement through open discussion. This classification was also guided by World Health Organization (WHO) best buys recommended interventions (23), where for each of the recommended interventions per each of the main NCDs risk factors were considered. We also assessed the progress of WHO recommended best buys Interventions in Rwanda. The interventions were graded fully implemented where they are written in the documents and have related programs and supporting environment interventions. They are graded inadequate if they are written in the documents but we lacked its related programs and supporting environment interventions.

For qualitative data (semi-structured key informant interview data), thematic analysis was performed using Atlas ti-7 (24). To get familiar with data, two researchers (JPN&DT) independently read both the interview transcripts and field notes. Using inductive approach, they (researchers) coded two first transcripts together to agree on coding framework. Then, the remaining transcripts were coded independently. Emerged codes and themes were discussed between the two researchers seeking to achieve consensus; a third researcher (JBN) was involved in this discussion and helped with conflict resolution. All authors reviewed and commented on the outputs of the analysis.

Ethical Considerations

All methods were performed in accordance with the ethical standards of the national research ethics committee and with the 1964 Helsinki declaration and its later amendments. The Rwanda National Ethics Committee approved this study (approval No.0025/RNEC/2019). Written consent was obtained from all participants, participation was voluntary and participants' confidentiality was assured at all steps of the study.

RESULTS

Generally, information from the desk review, the consultations, the semi-structured key informant interviews and the consultative workshop, were informative and complementary in providing insights regarding the aims of the study. The online search retrieved 178 documents of which, 18 documents (policies, laws, strategic plans, and Ministerial orders/instructions) describing population-level interventions targeting NCD risk factors were included. Sixty participants were visited at the workplace as part of the stakeholders' consultations (**Table 1**, left column). They provided information on programs and other population- level interventions beyond the identified

Participant Position	Number of participants	
	Consultations	Key informants interviews
Division manager	10	2
Managing director	3	1
NGO director	4	1
Program manager	10	1
District directors of the health unit	12	2
NCD alliance member	21	3
Total	60	10

policies from online desk review. Ten key informants were interviewed (**Table 1**, right column) and shared their perceptions regarding barriers and facilitators for the implementation of population-level interventions targeting NCD risk factors.

Population-Level Interventions Targeting Risk Factors for Diabetes and Hypertension in Rwanda

Online searches and stakeholders' consultations identified population-level interventions implemented in Rwanda, comprising policies, laws, ministerial orders, notices and instructions, programs, and supporting environment interventions. Rwandan health system consists of three level namely central level which consists of ministries and affiliated implementing agencies, district level is the point of implementation and it consists of district health unit, health committee and various partners including national and international governmental organization (**Figure 1**). Tis flowchart is not only applicable to health sector but others too. Policies are developed at central level, implementing agencies breakdown policies into actions (program and supporting environment interventions) and the implementation is done at district by district itself or in partnership with various partners over guidance and coordination of ministry affiliated implementing agencies. Community level consisted of sector leaders and health committee at the health center who serve as a liaison to the community members (beneficiaries). The policies, laws, ministerial orders, notices and instructions target most of the population categories countrywide. These are implemented through designing of specific programs and supporting environment interventions. Programs and supporting environment interventions are sometimes specific to a given category of people and may cover a sub-set of the country depending on the priority and the availability of required resources. Desk review only identified documents describing the implementation phase of the interventions, but we did not identify any documents describing their evaluation. Depending on the risk factor considered, the concerned ministries and its partners established and coordinated the implementation of the respective interventions; for example, interventions targeting physical inactivity were established by the Ministry of sports

(**Table 2**). The NCD Policy (25) and its Strategic Plan (26) (July 2014–June 2019), as well as the Fourth Health Sector Strategic Plan (27) of 2018–2024, provide overall guidance and strategies to tackle risk factors for diabetes, hypertension, and NCDs in general. The NCD policy is the main guiding document for most of the population-level interventions and defines the respective roles of each of the concerned stakeholders.

The National School Health Policy (28) targets students in pre-primary, primary, and secondary schools with respect to different health problems diseases, including NCDs. These four policies cross-cut across multiple risk factors, including unhealthy diets, physical inactivity, tobacco use, and harmful use of alcohol. Interventions specific to each of these four major NCD risk factors are presented in the following paragraphs. **Table 2** below summarizes the cross-cutting interventions as well as the interventions targeting specific NCD risk factors.

Interventions Targeting Unhealthy Diet

We identified three policies targeting unhealthy diet through the online searches, namely the National Early Child Development Policy, the National Agriculture Policy and the National Food and Nutrition Policy. The National Early Child Development Policy aims to reduce malnutrition and stunting among below 6 years old children. The National Agriculture Policy addresses food and nutrition security in the community through education and awareness programs focusing on food production, whereas the National Food and Nutrition Policy focuses on providing strategies to improve knowledge and capacity of households for food and nutrition security in food insecure areas. Through the consultations, we identified various community-based activities aiming to enhance knowledge and skills of the population related to the preparation and consumption of a healthy diet. These include, for example, media dialogues with nutritionists and health professionals, especially during nutrition week. Healthy diet education was integrated into the existing community programs, such as the monthly community work usually known in the local language as "Umuganda." The Baho Neza "live healthy" program is an integrated campaign aiming to ensure healthy and happy families; as part of this program, families are taught to prepare healthy diets. A healthy diet is part of the curriculum in primary and secondary schools. Training of nutritionists and other health care providers enables them to educate the population about a healthy diet at both health facilities and the community level.

Interventions Targeting Physical Inactivity

We identified three policies targeting physical inactivity. The Prime Minister's Instructions No 001/03.0/03/03/2012 of 03/03/2012 (29) and the Ministerial order No 02/mifotra/15 of 09/06/2015 (30) enforce the participation of civil servants in physical activity by determining time and facilitation for physical activity. The Sport development policy (31) promotes sports talent detection, school, and sports among the general population (**Table 2**).

Through the stakeholder consultations, we identified various campaigns for community participation in physical activity. Identified activities include the bimonthly physical activity

FIGURE 1 | Flowchart of population-level interventions implementation in Rwanda.
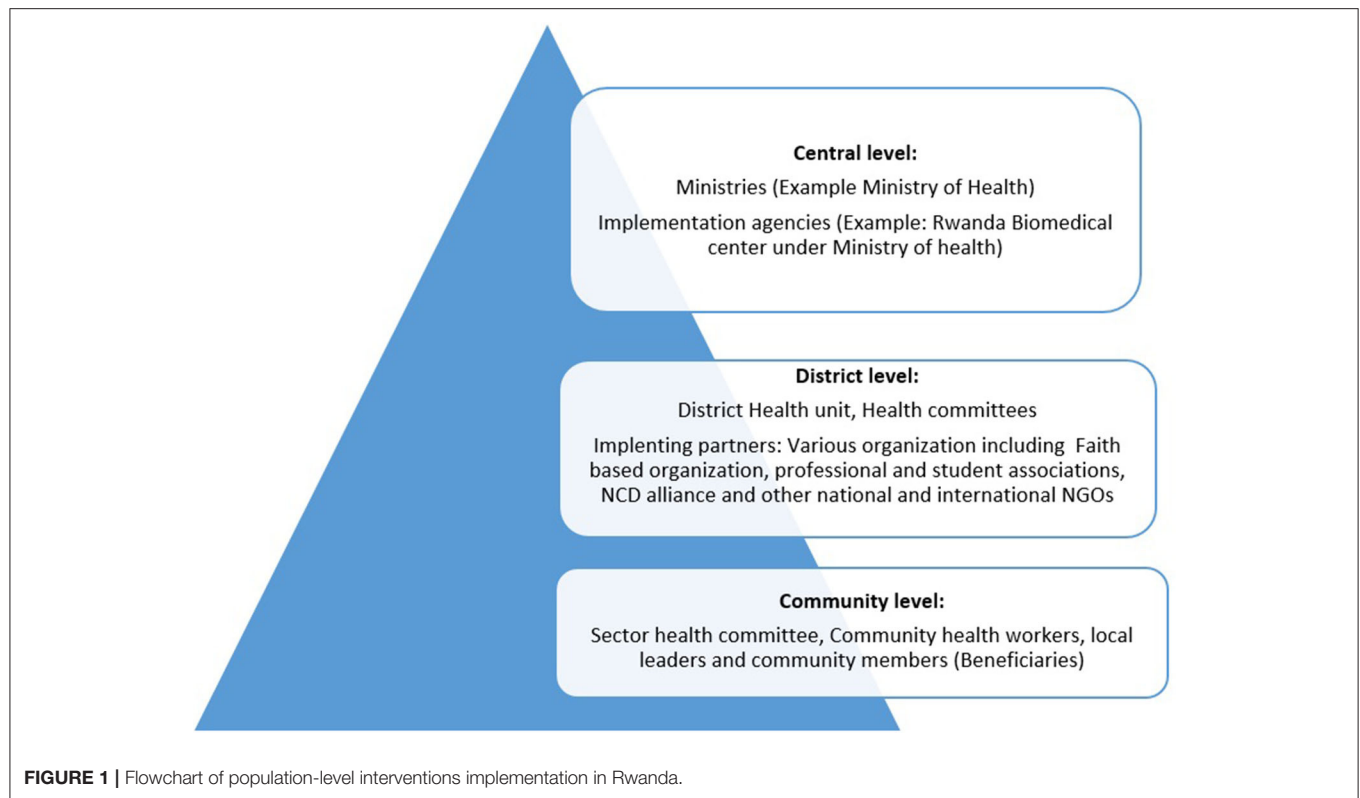
campaign known as "car-free day," which was initiated by the city of Kigali in 2016 and is currently being extended to most other cities and towns in the country. During this campaign, cars and motorbikes are stopped from using main roads in the city/town from 7 a.m. to 10 a.m. to allow people to exercise freely at the designated grounds with guidance by experienced facilitators. Sports competitions between public and private institutions such as schools, the army, the police, ministries, and government administrative entities are also common. For example, the Umurenge Kagame cup is a sport competition (mainly football) financed by the President of the Republic of Rwanda His Excellency Paul Kagame. Mass media, mostly via television and radio, also serve to increase community awareness about physical activity and to encourage individuals to become physically active. Car-free free zones created in the cities, exercise grounds, and roads with side walkways for pedestrians represent supportive infrastructure for physical activity. Training of facilitators and establishment of units in charge of physical activity has occurred in most public institutions in Rwanda. Public servants are given 2 hours and related facilitation to participate in physical activity every Friday from 3 p.m. to 5 p.m.

Interventions Targeting Tobacco Use

Since 17 January 2006, Rwanda has become part of the WHO Framework Convention on Tobacco control and has established various policies targeting tobacco use and, in some cases, also address harmful substances beyond tobacco. Six policies were identified through the online search (**Table 2**); these include laws,

ministerial orders/instructions, and public notices. Instructions of the Minister of Health N° 20/10 of 10/05/2005 (32) intends to protect both non-smokers and the environment from the hazardous effects of public smoking through the promotion of smoke-free spaces and designated smoking spaces, as well as designing visible messages prohibiting smoking in public places. Law N° 08/2013 of 01/03/2013 (33) aims to limit the availability of tobacco, promotes the creation of smoking-free environments, and prohibits the illegal production and trade of tobacco in Rwanda. This law limits the quantity of tobacco for travelers entering Rwanda (this is restricted to 200 cigarettes or cigarillos or 50 cigars or 1 kg of tobacco), and recommend all activities related to tobacco production must be authorized by the Ministry of Trade and Commerce. The law prohibits all tobacco sponsorship and promotion. As part of limiting tobacco accessibility, the law establishing the excise duty (34), which states that tobacco is taxed at 36% of the retail price of a pack of 20 rods plus 130 FRW per pack. Furthermore, Law N°03/2012 of 15/02/2012 (35), regulates the use of narcotic drugs and psychotropic substances and precursors in Rwanda. In addition, the Ministerial order N° 20/33 of 09/06/2015 (36) aims to protect non-smokers and the environment. Places intended for public gatherings such as schools, hospitals, workplaces, pharmacies or sports facilities are designated smoke-free. This order requests that owners of public spaces establish smoking areas with clear warnings against public smoking.

The Ministerial order N° 20/34 of 09/06/2015 (37) regulates the design of health warning messages on tobacco packages.

TABLE 2 | Population—level policy interventions targeting risk factors for hypertension and diabetes being implemented in Rwanda.

Targeted risk factors	Policy	What it covers	When it was established	Coordination leader	Target population	Coverage	Evaluation status
Cross-cutting policy interventions targeting all 4 risk factors unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol	Non-Communicable Disease (NCD) Policy	This Policy provides guidelines and strategies to target all NCDs risks factors.	2015	Ministry of health and Rwanda Biomedical Center (RBC)	All age categories	Countrywide	Not evaluated
	Rwanda NCDs national strategic plan		2014–2019		All age categories	Countrywide	Not evaluated
	4th Health Sector strategic plan (HSSP IV)	HSSP IV is the guiding document that focuses on several interventions against various NCDs risk factors such as reinforcement of laws on tobacco and alcohol, promotion of physical activity and healthy diet	2018–2024	Ministry of health	All age categories	Countrywide	Not evaluated
	National school health policy	The National school health policy targets pupils from pre-primary to secondary schools to improve their learning outcomes. It guides various interventions targeting unhealthy, such as nutrition education, and physical activity promotion as well as prevent alcohol, tobacco and drug abuse prevention interventions.	2014	Ministry of education	Schooling children	Countrywide	Not evaluated
Policy interventions targeting unhealthy diet	National Food and Nutrition policy (NFNP)	This policy focuses on providing seeds for vegetable and fruits as well as the planting guidance. Provides a framework for food in emergencies and supports schools' feeding programs.	2013–2018	Social cluster ministries led by Ministry of health, Ministry of agriculture and animal resources, Ministry of education, Ministry of gender and family promotion and Ministry of local government	All age categories	Countrywide	Not evaluated
	National Early Childhood Development (NECD) policy	Focuses on combating malnutrition through different initiatives such as a program providing a cow per family, provision of fortified food to some households, and promoting fruit and vegetable farming at the community level through kitchen and village gardens.	2016	Ministry of gender and family promotion	Children from 0 to 6 years	Countrywide	Not evaluated
	National agriculture policy	This policy provides guidance on different nutritional awareness, education programs and availing bio-fortified food, promotion of kitchen gardens for vegetables and fruits, distribution of livestock in needy households.	2018	Ministry of agriculture and animal resources	All age categories	Countrywide	Not evaluated
Policy interventions targeting physical inactivity	Ministerial order N°02/Mifotra/15 of 09/06/2015	To establish mandatory 3–5 p.m. weekly reserved for physical activity in public service.	2015	Ministry of Labor and Public Services and the Ministry of Sports	Public servant	Countrywide	Not evaluated
	Prime Minister's Instructions no.001/03.003/03/2012 of 03/03/2012		2012		Public servant	Countrywide	Not evaluated

(Continued)

TABLE 2 | Continued

Targeted risk factors	Policy	What it covers	When it was established	Coordination leader	Target population	Coverage	Evaluation status
	Sport development policy	Provides guidelines for various interventions targeting physical inactivity; this includes the initiation of different physical activities across the different population categories, ensures required infrastructures and resources	2012	Ministry of Sports	All age categories	Countrywide	Not evaluated
Policy interventions targeting tobacco use	Ministerial order N°20/34 of 09/06/2015 determining the content and design of the warning put on the package of tobacco and tobacco products	This order determines the contents and design of the health warning messages on tobacco and related product packaging.	2015	Ministry of health	All age categories	Countrywide	Not evaluated
	Ministerial public notice banning Shisha ban	This notice warns the public against the use, advertisement and importation of water pipe tobacco known as shisha effective from 15/12/2017.	2017	Ministry of health	All age categories	Countrywide	Not evaluated
	Law governing narcotic drugs, psychotropic substances and precursors in Rwanda N°03/2012 du 15/02/2012	This law regulates the production, processing, distribution and use of narcotic drugs, psychotropic substances and precursors in Rwanda.	2012	Ministry of Justice	All age categories	Countrywide	Not evaluated
	Instructions of the minister of health N° 20/10 of 10/05/2005 relating to the protection of non-smokers and the environment against the effect tobacco use	These instructions intends to protect both non-smokers and the environment against the hazardous effects of public smoking. Prohibit public smoking and advises pregnant and breastfeeding women against smoking. It ensures the tobacco waste products and residuals proper disposal to avoid environmental destruction.	2005	Ministry of health	All age categories	Countrywide	Not evaluated
	Ministerial Order determining the characteristics of smoking areas and the content included in the notice displayed in the smoking area N° 20/33 du 09/06/2015	This order defines the design of smoking areas and the protection of non-smokers and obliges the establishment of places reserved for smoking with clear warnings against public smoking.	2015	Ministry of health	All age categories	Countrywide	Not evaluated
	Law relating to the control of tobacco N°08/2013 of 01/03/2013	It intends toestablish smoking free environments and prohibits the illegal trade and production of tobacco by certification of tobacco to be legally used in Rwanda.	2013	Ministry of Justice	All age categories	Countrywide	Not evaluated
Policy interventions targeting harmful use of alcohol	No specific policy available	-	-	-	-	-	-

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Through this order, all tobacco sold on Rwandan territory is packaged and labeled with clear health warning messages, such as smoking kills, causes cancer, heart diseases, and other health conditions such as impotence, infertility, miscarriages, and stroke. A Ministerial public notice bans water pipe tobacco known as shisha (38) on Rwandan territory.

The stakeholder consultations identified several programs that aim to increase tobacco cessation. Large public awareness campaigns sensitize the community about the health dangers associated with tobacco use. These are delivered through multiple channels, including the media, mass sports campaigns, and community meetings. Medical students and professional associations are involved in campaigns against tobacco use. In secondary schools, anti-tobacco and drug abuse clubs were established. These clubs help to raise awareness of tobacco harm and cessation both at school and in the community.

Interventions Targeting Harmful Use of Alcohol

No specific policy intervention regulating harmful use of alcohol was found through desk review. However, we identified four cross-cutting policies (**Table 2**) that target harmful use of alcohol and many more NCDs risk factors in Rwanda. The law establishing the excise duty (34) states that local beer and exported beer are taxed at a rate of 30 and 60%, respectively. Local and imported wines are taxed at a rate of 30 and 70%, respectively while brandies, liquor, and whisky are at a rate of 70%. The stakeholder consultations identified different programs and other preventive interventions targeting the harmful use of alcohol. There are various awareness campaigns to sensitize the community about health hazards associated with the harmful use of alcohol through mass media (radio, television). These same campaigns are also integrated into existing local communication channels, for example through villages meetings, during monthly physical activities campaigns, and after community activities. Through stakeholders' consultations, we identified multi-sectoral operations consisting of different government institutions, namely police, local authorities, regulatory authorities, and staff in charge of health at different levels, jointly identify and ban non-standardized alcohol production and consumption.

As illustrated in **Table 3**, Rwanda has implemented most of the WHO bet buys recommended interventions targeting tobacco use and physical activity. For the harmful use of alcohol and unhealthy diet, however, there is inadequate implementation of the recommended interventions. For the harmful use of alcohol, these limitations relate to access to retailed alcoholic beverages and alcohol advertisement. For unhealthy diet, there are no interventions to reduce salt intake in food or to promote the replacement of trans-fat food.

Participants representing each of the institutions that participated in this study attended the one-day stakeholders' consultative workshop. The preliminary findings from the situational analysis were well-received and validated. All participants generally agreed with the findings and provided constructive inputs. For example, they all agree on the lack of specific policies targeting harmful use of alcohol.

Perceived Barriers and Facilitators for the Implementation of Population-Level Interventions Targeting NCD Risk Factors

Ten key informants shared their perspectives and experiences related to implementing population-level interventions. All interviewees confirmed that Rwanda has implemented various interventions targeting risk factors for diabetes and hypertension. They agreed that various obstacles hinder the implementation of different population-level interventions. They openly shared their perception of the barriers as well as what they think can facilitate the implementation of population-level interventions targeting diabetes and hypertension. The findings are classified in twelve themes emerged from the analysis, seven of which represent perceived barriers and five of which represent perceived facilitators. These themes, along with supporting quotes from the key informant interviews, are presented in the following paragraphs.

Perceived Barriers to the Implementation of Population Level Interventions

Limited Knowledge and Misbeliefs About Ongoing Interventions and Targeted Risk Factors

Some of the ongoing prevention activities are misinterpreted among the general population, which may be a reason for low community participation. For instance, physical activity interventions are considered to target only people who have excessively eaten and/or want to lose weight. Similarly, some people still believe that being overweight is a sign of high socio-economic status, instead of being among the risk factors for diabetes and hypertension. These misbeliefs about ongoing interventions and targeted risk factors among the population pose a great barrier to the implementation of population-level interventions.

"You will meet people in the community who still think that a man with a big tummy is rich and is eating well whereas others think that doing sport is just for overweight people who want to reduce weight" (KIIP8).

Insufficient Mobilization of the Community

Some of the interviewed key informants said that there are plenty of good ongoing population-level interventions targeting risk factors for hypertension and diabetes, but the community is not well mobilized about these interventions to attract their participation, which is a barrier to their successful implementation and scale up to the community level. For example, on physical activity interventions, they (interviewees) urge that using phone short messages to mobilize the community for participation is not enough and does not reach every one especially those who do not own cell phone. They reported a lack of local leader's efforts to mobilize the whole community to get involved in ongoing population-level interventions is a barrier to physical activity participation.

"Physical activity is a good intervention that can be scaled up at community level countrywide but in addition to the messages spread by different people, have you ever seen local leaders

TABLE 3 | Current implementation of 'WHO Best Buy' Interventions in Rwanda.

Risk factors	WHO Recommended best buys Interventions	Progress
Tobacco use	Tax increases	Fully implemented
	Smoke -free-indoor workplace and public places	Fully implemented
	Health information and warnings against tobacco use	Fully implemented
	Bans on tobacco advertising, promotion and sponsorship	Fully implemented
Harmful alcohol use	Tax increases	Fully implemented
	Restricted access to retailed alcohol	Inadequate
	Bans on alcohol advertising	Inadequate
Unhealthy diet	Reduced salt intake in food	Inadequate
	Replacement of trans fat with polyunsaturated fat	Inadequate
Physical activity	Public awareness campaigns through mass media on physical activity combined motivational and environmental programs aimed at supporting behavioral change of physical activity levels	Fully implemented

mobilizing those poor people about car-free day to participate? Messages spread by local leaders and community health workers have a big influence on the community therefore they should be involved to mobilize community participation in physical activity" (KIIP6).

Lack of Consistency on the Implementation of Friday Physical Activity Across Institutions

One key informant highlighted issues related to Friday Physical Activity specifically. One issue is that not all public institutions provide sport facility subscription to their employees. Additionally, targeting only the public sector with this intervention may be too restrictive, when many other individuals could potentially also benefit.

"In some public institution, Friday sport is not done and no facilitation is provided whereas others do, secondly, why this intervention is for public servants only while there is a great number of Rwandans working for private institutions?" (KIIP10).

Limited Collaborative Efforts From All Involved Stakeholders

Targeting risk factors for diabetes and hypertension requires efforts from all relevant stakeholders; however, some key-informants from non-health domains were doubtful of their relevance and insisted that Ministry of health deals with all diseases and related issues. This is indeed a great barrier to implementation of population-level interventions targeting risk factor for hypertension and diabetes since most of these risk factors cross-cut across different sectors. Lack or limited collaborative effort to implement these interventions was identified as a barrier to successful implementation.

"But I think that is Ministry of Health's mandate, for us, we only deal with food production and their consumption but diseases are dealt by the Ministry of health" (KIIP3).

Conflicts Between Commercial and Public Health Interests

Through various marketing strategies (e.g., betting games, music, shows, and films), industries encourage people to consume beer, tobacco, sugar sweetened beverages and energy drinks. Public health actors, on the other hand, have fewer resources and use routine ways of mobilizing people to live healthy. The influence of this kind of commercial competition is a threat to the implementation of population level intervention targeting alcohol, tobacco and other unhealthy products.

"You will see many youths attending new beer promotion shows because they have used expensive and attractive ways of marketing; such ways are difficult for us who are protecting them from NCDs. Regarding tobacco, there is also an expensive way of marketing tobacco in the movies using celebrities which then entices people, especially youth, to imitate them," (KIIP6).

Lack of Adequate Funding for Implementing Population-Level Interventions

Human and financial resources as well as related logistics are required for implementing population-level interventions. Due to a lack of required resources, some interventions are partially implemented. Many interventions are designed to have a countrywide coverage; an interviewed participant reported that they are imposed to implement this in some parts of the country due to resources constraints. Additionally, healthy food is expensive; for example, eating fruits and vegetables is highly recommended for healthy diet, yet they are among the most expensive food types in Rwanda, which makes it difficult to recommend them to the population.

"It is shameful to tell people to eat fruits when you know that they cannot afford them because of the high cost. The same for some programs; we prefer to implement them in some districts because of financial constraints" (KIIP4).

Limited Policy Enforcement of Population Level Interventions

Lack of follow-up and policy reinforcement was reported as barrier to successful implementation of population-level interventions. Interviewed participants reported that some interventions (policies or programs) are not well implemented due to limited enforcement by implementers, which is perceived as a barrier to their success. For example, public servants are given paid hours for physical activity but some prefer to use this time for different purposes because there is no or limited enforcement.

> "Almost all public servants are given time for physical exercise and are subscribed to the nearest physical exercise facilities but they opt to go for their own businesses during physical activity hours, and those are people who are paid hourly by the government but I have never seen anyone asked to explain why not attending physical activity" (KIIP5).

Likewise, regardless of the progress to date about tobacco use, some people smoke in public and are not condemned for doing, which shows a weak policy reinforcement. This is a barrier to the protection of non-smokers and the environment in general against tobacco and related hazards.

> "There is an improvement for public smoking reduction but since we do not see people sanctioned for smoking in public; it will still be a problem," (KIIP7).

Perceived Facilitators for the Implementation of Population Level Interventions

Paying Special Attention to Higher Risk Groups, Such as the Elderly

Some groups of people, such as the elderly, are more exposed to and burdened by NCDs than others; these population groups, however, are not sufficiently targeted. Having strategies to locate and engage the elderly in ongoing population-level interventions could make a remarkable improvement.

> "Due to their age, old people are vulnerable to most NCDs, they have little strength to go for physical activity, limited medical assistance, they stay at home alone and some of them will tell you that they prefer to die instead of quitting alcohol or tobacco. I truly think this category needs special help. If we are aware of people who are at risk of developing a disease, what do we do to protect them? What do we do to reduce their agony? We do not have these interventions targeting them, for example, there should be a community health worker in charge of NCDs to group old people per village and schedule a regular education session targeting to engage them in population-level interventions. This should be done in an organized way and be reported to make sure they are done progressively" (KIIP9).

Strengthened Community Awareness Campaigns of the Ongoing Interventions

Educating individuals on the risk factors for diabetes and hypertension and how to prevent the diseases will likely enhance compliance and facilitate the implementation of population level interventions. Most participants reported that individuals should be educated about the risk factors from early childhood to mitigate misconceptions. Interviewed participants highlighted specific modalities, such the use of multiple strategies for community awareness campaigns such as through regular and locally known dramas or church leaders, which could improve the impact of health messaging in the community.

> "It is about educating the population regarding the interventions and when they understand their roles and responsibility; they will surely comply and this will lead to an increased impact. Church leaders, schools, and radio-based famous drama like urunana and musekeweya (Kinyarwanda named dramas) are good communication channels to reach many people" (KIIP9).

Strengthened Multi-Sectoral Collaboration and Strengthen Stakeholders' Involvement in Designing and Planning Population-Level Interventions

Risk factors for diabetes and hypertension cut across multiple sectors and cannot be managed by health sector alone. Participants emphasized the importance of engaging these multiple stakeholders in designing, planning and implementing population-level interventions. Each stakeholder (ministry and government agencies as well as NGOs and other private sector institutions should have play their specific role in NCDs prevention.

> "Each of the related ministries and institutions has a role in preventing NCDs; for example, laws prohibiting public smoking: Rwanda revenue authority intervenes by increasing tobacco-related products taxes and ministry of health by providing coordination. Ministry of education in partnership with Ministry of health can help in strengthening NCD prevention teaching from primary to the secondary schools" (KIIP4).

Increased Funds Allocated to Population-Level

Most of the interviewed participants reported limited resources allocated to population level interventions. Implementing agencies should have sufficient budget allocated to awareness campaigns in the community and different NCDs screening. Government should be attentive to NCDs burden and avail sufficient budget to run different ongoing population-level intervention targeting NCDs risk factors.

> "I don't know how much the government allocates in the health sector, but prevention of non-communicable diseases requires sufficient resources to reach the whole community" (KIIP2).

Reinforced Policy Interventions Targeting Tobacco Use and Harmful Use of Alcohol

There are number of laws regulating production, importation and distribution of tobacco and alcohol. Interviewed participants insisted that such laws should be reinforced in order to better control concerned risk factors. For example, a participant suggested that any kind of advertisement for alcohol, tobacco and any risky products should be abolished to facilitate their control; otherwise, it is difficult to convince the community about their

harmfulness of them when they being publically advertised in the country.

"You cannot convince people that alcohol is dangerous when it is being advertised in different ways, laws against alcohol advertising should be established and applied" (KIIP6).

DISCUSSION

In response to the increasing burden of NCDs, this study identified and described population-level interventions in Rwanda targeting risk factors for diabetes and hypertension, as well as perceived barriers and facilitators for the implementation of these interventions. The NCD policy was identified as the main policy targeting risk factors for diabetes and hypertension, and other identified policies included those related to food and nutrition, physical activity promotion, and tobacco control. Most WHO best buy interventions targeting tobacco use and physical activity have been adopted, while those targeting harmful use of alcohol and unhealthy diet were inadequately implemented.

This study identified multi-layered and multiple-component interventions targeting unhealthy diet. The promotion of village and household gardens for the growing of vegetables and fruits was one such intervention identified. These interventions were primarily initiated targeting malnutrition than actually NCD, for example the kitchen garden aims to combat malnutrition among children but can indirectly target unhealthy diet as NCDs risk factor. Studies have revealed that the promotion of vegetable and fruits production has been effective in reducing population exposure to unhealthy diets (39) and agricultural policies increase healthy food production and accessibility (40), and reduce its cost at the market (41). Nutrition education in schools has been effective in promoting students' healthy diet habits in other studies (42). Salt reduction is a key intervention targeting unhealthy diet and one of the WHO best buy interventions targeting (43), however, no related interventions were identified in this study. This was similarly reported in the recent NCDs Diseases Progress Monitor 2022 (44) where implementation of best buys recommended intervention targeting unhealthy diet were partial or inadequate. As country progresses to ensure reduction of poverty and malnutrition, unhealthy diet as a risk factor need to be particularly considered.

Regarding physical inactivity (PA), different campaigns identified in Rwanda focused on mass media, school sport competitions, mass sports campaigns, and the construction of physical activity infrastructures in the community. This study found strong government willingness to set up policies and a supporting environment to encourage physical activity through different initiatives, such as community mass sports campaigns known as car-free day, Friday physical activity for public servants, and different inter-institutional as well as school sport competitions. Similar interventions have worked worldwide (45) and are in line with WHO best buys recommended interventions targeting physical inactivity (43).

Concerning interventions targeting tobacco smoking in Rwanda, we identified interventions aimed at raising community awareness of the dangers of tobacco use, restricted access to tobacco and creating smoke-free areas. These interventions are all in line with WHO best buys recommendations for tobacco control. This study observed a political willingness to address tobacco as a risk factor, through the formulation of tobacco control laws, civil society involvement in anti-tobacco campaigns, and public education about tobacco use-related health risks. These findings support what is reported broadly; for example, It has been shown that involving different sectors in implementation of interventions targeting tobacco use is an important factor for their success (46), and that education combined with other measures such as excise taxes and prices on tobacco products help to encourage smoking cessation (47). This study identified no specific policies targeting the harmful use of alcohol but identified cross-cutting policies with relevant components. Such components include, for example, awareness campaigns emphasizing the health risks of harmful use of alcohol, and banning non-standardized alcohol production. A lack of sufficiently coordinated policies targeting the harmful use of alcohol will likely allow alcohol industries to promote, market, and lobby their products (48, 49).

All identified population-level interventions in this study were not evaluated. An evaluation is essential part of interventions to monitor the intended objectives and for a better planning. Through some of these interventions were newly introduced, there other which would have been evaluated. Most of the interventions target all age categories of the population with countrywide coverage. This ensure that every one can benefits from these interventions, however, few interventions such Friday physical activity intervention only target subset of the population, this can be scaled up to benefits more people. We identified different barriers perceived to be hindering the implementation of some population-level interventions.

Inconsistency in implementing physical activity interventions across different settings was identified as a barrier. A scarcity of resources, the nature of work for policymakers, who are juggling countless responsibilities and priorities, and the lack of exposure to the relevant burden may be linked to this inconsistency. People in cities, for example, are on average more exposed to sedentary life than those in rural areas (17); this may explain why some interventions, such as those promoting physical activity, are more prevalent in urban. However, successful interventions are being scaled countrywide. Car-free day, for example, started in Kigali city and is currently being scaled up to promote physical activity across much of the country.

Limited policy enforcement was identified as a barrier, especially linked to tobacco use, similar to a study assessing tobacco control in 17 HICs and LMICs that ratified the Framework Convention on Tobacco Control (FCTC), which found a weak implementation of tobacco control policies, particularly in developing countries (50). Research conducted in 16 countries found significantly more tobacco advertisements and outlets in LMICs compared with HICs (51). Tobacco smoking is still common throughout entertainment (music and video clips) in Rwanda. Commercial interests of tobacco industries negatively affect tobacco control policies (52). Overall, limited knowledge and misbeliefs about ongoing interventions and targeted risk factors was reported as a barrier to

implementation of various population-level interventions. This barrier may be linked to central planning and low community involvement in designing and planning of these interventions. Insufficient mobilization of the community was reported as a barrier to implementing population-level interventions, this indeed lead to low involvement and buy in by the community members. In Rwanda, due to scarcity of medical and public health professional (53), there might be not enough people equipped with sufficient knowledge about available to mobilize the community about ongoing prevention interventions targeting diabetes and hypertension. Limited knowledge and misbelief may lead to low buy-in by the community and hinder the effectiveness of the concerned intervention. The literature recommends cooperating with the population when designing population-level interventions to ensure culturally adapted and understandable interventions (54).

Weak collaboration among various stakeholders was identified as a barrier to the implementation of population-level intervention targeting risk factors for diabetes and hypertension in Rwanda. This finding was similarly found in various settings such as in Kenya, Malawi, and Mauritius (55, 56).

Lack of NCD units or focal persons in non-health sector institutions might lead to this weakness. Coordination of all involved sectors to monitor individual stakeholders' roles and contributions toward preventing various risk factors would likely lead to improved control of NCDs at the population-level.

Limited funding was also a barrier to the implementation of population-level intervention targeting risk factors for diabetes and hypertension. This likely plays a role in the inconsistent and partial implementation of some interventions. According to Rwanda NCDs strategic plan (2014–2019), NCD prevention in Rwanda is generally underfunded (26) and was commonly reported in other settings (57, 58).

This study found a number of perceived facilitators which could be considered to improve for population-level interventions implementation. Special attention paid to interventions explicitly designed to protect the elderly, as they experience the highest burden due to NCDs. Thus focusing on high-risk population groups, such as the elderly, is likely a facilitator for effectively addressing NCDs in Rwanda. Interventions to improve physical activity (59) and home-based strategies encouraging fruits and vegetable consumptions (60) specifically among the elderly have been implemented successfully, for example in South Africa and the United States, and could be model for adaption in Rwanda or elsewhere. Strengthened community awareness campaigns and strengthened multi-sectoral collaboration and strengthen stakeholders' involvement in designing and planning of the ongoing interventions is essential and would be of a great importance to rise community and stakeholders knowledge and engagement in on going intervention. It is indeed reported as a key to successful implementation of NCDs prevention interventions in other settings (61, 62). Training and involving more community members in design and implementation of these intervention would be a locally made solution to limited health professionals involved in these activities. Since NCDs risk factors cross cut across different sectors, strengthened

multi-sectoral collaboration is widely recommended to facilitate the implementation of population-level interventions targeting NCDs (63). Increased funds allocated to population-level was reported a facilitator for implementing population-level interventions, various studies revealed the role of funding in NCDs preventions (64, 65). The budget allocated for health sector has been revised upward over the past 5 years (66), which shows the government willingness to respond to health issues in the country including the most emerging NCDs. Reinforcement of policy interventions targeting tobacco use and harmful use of alcohol was perceived as a key facilitator to their implementation. Few interventions targeting harmful use of alcohol were identified in this study, which shows a need for reinforcement. The same for tobacco, public smoking was reported to be practiced with no rigorous prevention measures. Filling the gaps between policy and their implementation is the ideal way to successfully prevent NCDs risk factors (67).

This situational analysis comprised a desk review, which included an online search as well as consultations with stakeholders, key informant interviews, and a consultative workshop. We defined the methods a priori and conducted each step with methodological rigor; however, there were some study limitations; searches only focused on a single governmental website to locate policy documents. It is possible, that other documents exist that we did not identify. However, we supplemented these searches with input from stakeholders, who are also familiar with the policy landscape in Rwanda. Regarding the key informant interviews, only 10 key informants were interviewed; in selecting these key informants, however, we aimed to ensure that multiple and differing perspectives important for the design and implementation of population-level NCD interventions would be captured. Talking to the community as direct beneficiaries for the population-level interventions would possibly identify further barriers and facilitator beyond implementers' perspectives.

CONCLUSION

This situational analysis of current population-level interventions, as well as perceived barriers and facilitators affecting the implementation. Various interventions are implemented, their evaluation is needed to monitor the effectiveness. While barriers and facilitators have been reported, these findings provide useful input to inform the strengthening of the public health response to diabetes and hypertension in Rwanda.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Rwanda National Ethics Committee Approval

No. 0025/RNEC/2019. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JPN and DT were involved in protocol development, data collection, analysis, conception, and successive revision of the manuscript. SN, JBN, and GU were involved in protocol development, data collection and analysis, reviewed, and added inputs in the manuscript. CB, JCB, SR, and TY were involved in protocol development, reviewed, and added inputs in the manuscript. ER and JB were involved in protocol development (methodology), reviewed, and added inputs in the manuscript. All authors contributed to the article and approved the submitted version.

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United States' Infrastructure Bill Contains Hidden $15 Billion Investment in Violence Prevention: Lead Abatement

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Recently, the United States' Congress passed and President Joseph Biden signed a long-anticipated, bipartisan, "Infrastructure Investment and Jobs Act" (1). The legislation includes ∼$1 trillion for infrastructure updates and modernization. Although many have focused on its funding for transportation projects, namely roads and bridges, there is another rarely discussed benefit the bill is likely to provide: reducing community violence. That is because the final bill included $15 billion dedicated to lead pipe removal.

Lead is a naturally occurring heavy metal that until recent decades was commonly utilized in gasoline, household paint, and water service lines. We now know that lead is a poisonous metal and a devastating neurotoxin. This knowledge led to governmental actions that forbids lead content in all three sources (2). In the population of gunshot survivors, retained bullet fragments act as a source of direct toxicity as well (3). Despite this understanding, the United States still maintains a water supply that utilizes 6.1 million lead service lines today (4). The result is an ongoing public health problem.

It may seem odd to think of lead pipes and violent crime as linked, but evidence indicates that exposure to lead in childhood is a risk factor for violence later in life (5, 6). This should not be surprising as the effects of lead on brain development are well documented in the scientific literature. Specifically, lead affects the development of children's cerebellum, hippocampus, and prefrontal cortex. These are areas of the brain that are critical for cognition, behavior and memory.

Although causes of violence are multifactorial, including issues as entrenched as poverty, racial inequity, and disparities in policing and education, violent crime is often an impulsive act. Given the neurocognitive effects of lead exposure, it is no surprise that research has shown an association between lead exposure and criminal justice system involvement (7). Robust data from the economic literature provides convincing evidence of the causal effects of the toxins on risky, antisocial behaviors, such as violence (5). Taken together, many experts now consider prior lead abatement measures to be a significant component of the "Great American Crime Decline" of the 1990s (8).

To be clear, combatting community violence in our communities will require a "health in all policies" approach to address the deeply entrenched racial inequities. While childhood lead exposure is a notable risk factor for violence, it is not the primary driver. Decades of policy, rooted in structural racism, have progressively compounded the challenge. For example, research examining the effect of racial discrimination in the 1930s, commonly known as redlining, show persistent adverse effects on the social determinates of health, including elevated levels of gun violence nearly a century later (9).

A truly effective response to community violence will require a multipronged investment in these same communities to reverse the innumerable policy decisions and chronic disinvestment. These strategies range from traditional public health programming such as deploying violence intervention and prevention programs (10) to altering health system priorities through insurance policy (11). From an environmental health lens, the work of Dr. Eugenia South is instructive. By deploying place-based interventions, such as structural home repairs, to neighborhoods experiencing segregation and concentrated poverty, these targeted investments translated into decreases in assault and homicide (12).

Although only a portion of a comprehensive solution, environmental interventions represent an achievable component of violence prevention strategy. Specifically, lead abatement remains a significant opportunity for tangible public health benefits. Although prior measures, such as removal from gasoline provided broad public health benefits, remaining sources of exposure exacerbate significant health disparities. To date, Black children hold four-fold higher odds of being found to have an elevated blood lead level greater than U.S. Centers for Disease Control and Prevention recommendations compared to their White or Hispanic peers (13). With regards to lead service lines, the disparities appear to also occur geographically, with the U.S. industrial Midwest disproportionately utilizing remaining lead service lines (4).

The Infrastructure bill's funding for lead removal will allow municipalities the opportunity to provide targeted investments in previously underserved communities, especially communities of color. This allows for a strategic investment in both long-term health and safety.

Policymakers would be wise to consider unintended consequences as they distribute this funding. Baltimore City, which has captured escalating national attention for its rates of violent crime, serves as a case example. Due to the number of people living in poverty in Baltimore City, along with the aging stock of public, subsidized, and affordable housing, over 65,000 children were diagnosed with clinically significant blood-lead levels of serious concern between 1993 and 2013 (14). A large segment of this exposure was related to research projects that were conducted in the 1990s in which families with children were moved into homes with known lead levels in order to test abatement processes (15).

Later, lawsuits filed by those families claimed that they were targeted for participation because they were low-income, and that they were not made aware of the risks of exposure to lead prior to enrolling in the experiment (16). Additionally, landlords continued to knowingly and unlawfully sell and rent unabated homes to families who could not afford to negotiate or move. This resulted in financial settlements of ∼$300 million. One Baltimore lawyer, who handled more than 4,000 lead poisoning lawsuits over 30 years, stated that 99.9% of his clients were African American (17).

Clients who received settlements were awarded structured payments up to thousands of dollars per month, meant to be paid out over the course of the plaintiff's lifetime. Unfortunately, this structure allowed predatory financial institutions to target low-income, often desperate victims, which subsequently acquired the settlement dollars in return for immediate, pennies on the dollar lump-sum payments to the victims. As a result, what was intended as a method of restorative justice became diluted, with only transient benefit for those experiencing a lifetime of harm. This elevates the importance of further lead abatement in affected communities, as it impossible to reverse the effects of exposure and efforts to ameliorate these effects are flawed at best.

Taking these factors into consideration, the bipartisan Infrastructure Investment and Jobs Act's plan to spend $15 billion in lead pipe removal is a wise investment and the next logical step in addressing the difficult challenge of ubiquitous lead exposure. As policymakers and public health officials continue to embrace the treatment of violence as a public health issue, this approach stands as a textbook example of a well-thought out public health intervention. Although some benefits, such as educational achievement, will be evident in the near-term, future public health officials, decades in the future, are likely to discover that this historic investment in lead pipe removal resulted in significant violence reduction for generations to come.

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Patient safety culture awareness among healthcare providers in a tertiary hospital in Riyadh, Saudi Arabia

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Patient safety is a serious concern in the health care industry. To enhance patient safety, healthcare providers are expected to minimize accidental harm to patients and enhance the quality of patient-centered care. The main objective of this study is to explore the awareness of the patient safety culture among healthcare providers. It is further intended to assess key fields and factors that hinder patient safety adoption and determine the effects of demographic factors on healthcare providers' awareness of patient safety culture. This study applied a cross-sectional quantitative design. It was conducted in a tertiary hospital in Riyadh, Saudi Arabia. The participants consisted of all healthcare providers working in a specific tertiary hospital in Saudi Arabia. A random sampling technique was applied in this study. The study sample size was 409 participants. A valid and reliable questionnaire was used to collect the required data. The T-tests, ANOVA. And regression was used. The study found that there is a moderate level of patient safety culture awareness among healthcare providers. Moreover, the findings also revealed that the age group "31−40" showed statistically different awareness levels as compared to the "more than 50 years' age group" ($p = 0.012$). Also, this study has found that gender and education have a significant influence on the awareness level of patient safety culture while position and work area have no influence on the awareness level of patient safety culture among healthcare providers. Managers in healthcare institutions should develop speeder response plans and make them part of the patient safety culture. Institutions offering bachelor's degrees and postgraduate in nursing should pay more attention to the subject of patient safety. The government healthcare sector, together with the private healthcare sector, should continuously train healthcare providers on patient safety procedures to improve the patient safety culture. Healthcare providers should be encouraged to report errors made during diagnosis or treatments to avoid them in the future.

Introduction

Patient safety is a serious concern in the health care industry globally. Harm prevention against patients and patient safety translates to a healthy patient safety culture and quality patient-centered care within many healthcare facilities. Aswat et al. observe that highly performing healthcare organizations have a healthy culture of patient care safety (1). Given this, it is important for healthcare organizations to create and maintain healthy patient safety cultures, not only to deliver quality patient-centered care but also for the betterment of the organizations' overall performance. Kumbi et al. define patient safety culture as "the values shared among organization members about what is important, their beliefs about how things operate in the organization, and the interaction of these within a work unit and organizational structures and systems, which together produce behavioral norms in the organization that promote safety" (2). Thus, to achieve a healthy patient safety culture, healthcare providers need to be aware of the expected organizational beliefs, values, and norms to achieve quality patient-centered care.

Globally, all healthcare providers, including nurses, are vulnerable to committing different medical errors, consequently causing patient safety to be a critical issue in the healthcare industry. For this reason, enhancing patient safety can significantly help to improve the general outcomes in every healthcare setting. Despite the probability of healthcare providers getting harmed being low globally (one out of 300) (3). Alnasser et al. observe that the costs due to medication errors are approximately 42 billion USD per year (4). In Saudi Arabia, specifically, a research study by Eldeeb et al. reveals that many healthcare practitioners, including nurses, have reduced levels of patient safety (5). Similarly, Khalil and his colleagues observe that the most serious events within the Saudi Arabia healthcare industry are related to allergic reactions due to medication errors (6). However, they are seldom formally reported. For this reason, the Saudi Arabia healthcare industry needs a complete overhaul regarding patient safety culture awareness among healthcare providers.

Different research studies have attributed the vulnerability of patients and healthcare providers within the Saudi Arabia healthcare industry to wrongful medication to different threats. Multiple studies show that the main reasons for wrongful medication and other threats occur due to the difficulty or inability of patients to communicate with physicians, language barriers, and the lack of comprehensive divulgence of both treatment plans and medical conditions (7). Also, a study by Parija and Adkoli established that the difficulty or inability of patients to communicate with physicians and language barriers are risk factors of harm in the administration of opioid medications within Saudi Arabia communities (8). Moreover, the patient-doctor interaction issue is also highlighted in a study

by Alnasser et al. In Alnasser et al.'s study, it was established that most Saudi Arabia medical schools do not fully address the significance of patient-doctor communication in educational curricula (3). Furthermore, the healthcare industry in the region is highly dominated by foreign physicians.

There are many other breaches in the safety of patients in Saudi Arabia besides the difficulty or inability of patients to communicate with physicians and language barriers. For example, a study by Panagioti et al. attributes burnout among physicians to the occurrence of medical errors (9). Moreover, other research studies identify hygiene as an inhibiting factor to quality patient care and safety. For instance, research on gloving and handwashing practices by Basurrah and Madani established that poor handwashing practices among Saudi Arabia medical staff significantly compromise patient safety and the provision of quality patient care (10). These findings are also supported by Muller and his colleagues, who reveal that handwashing compliance practices among emergency department (ED) staff are approximately 29% (11). However, research by Alshammari et al. establishes that the compliance rate among the Saudi Arabia ED staff is at approximately 29% due to the departmental inability to implement hand hygiene protocols (12). Based on this finding, it is evident that Saudi Arabia's healthcare providers violate patients' safety protocols despite being cognizant of their implications.

Globally, patient safety is still a serious issue in the healthcare industry. To optimize patient safety, health care providers must minimize accidental harm to patients and enhance the quality of patient-centered care (13). Following the release of the Institute of Medicine's "To Err is Human" study in 1991, patient safety issues became more prominent. By that time, approximately 98,000 individuals perished each year due to hospital-related errors (1). The Institute of Medicine report emphasized the importance of patient safety and the need to hold clinicians and other health care providers accountable for irresponsible actions that put patients in jeopardy (14). Nevertheless, it was unclear how such healthcare inconsistencies would be addressed without causing conflict among healthcare workers, especially in terms of the reporting system (3). The Department of Health found that error prevention was a strategy that necessitated significant system-wide reforms centered on avoiding, identifying, and reducing harmful behavior in inpatients that could result in morbidity or mortality.

In population health, developing a healthy safety culture requires a thorough grasp of a society's cultural ideas, values, and norms. This knowledge helps healthcare executives identify attitudes and behaviors that should be encouraged, rewarded, or anticipated (3). For example, a critical examination of the situation in many healthcare systems has demonstrated the importance of focusing on organizational elements such as patient safety rather than individual wrongdoings. It was discovered that taking a cultural change approach to addressing patient safety issues yielded the best results in

increasing healthcare quality and safety (4). Instead of blaming culprits, healthcare systems are urged to consider mistakes as opportunities for quality and safety advancements.

Culture is the sum of a population's attitudes, societal practices, experiences, and values that guide their overall behavior. The importance of being committed to discussing and learning from mistakes is emphasized in establishing safety culture (12–14). Such a culture recognizes the inevitability of mistakes and aggressively discovers hidden hazards while adding non-punitive ways to report errors and analyze potential negative outcomes. Cultural safety in the Saudi Arabia healthcare sector is similar to the concepts mentioned above. A research study by Eldeeb et al. reveals that many Saudi Arabia healthcare practitioners, including nurses, have reduced levels of patient safety. As a result, they do not officially file their reports on adverse events (11).

Similarly, research by Khalil and his colleagues observes that the majority of prevalent serious events within the Saudi Arabia healthcare industry are related to medication errors (4). However, they are seldom formally reported. These findings emphasize the need for improvements in the Saudi Arabia healthcare industry regarding patient safety culture awareness among healthcare practitioners.

More research works to assess the patient safety culture among Saudi Arabia health care practitioners, including pharmacists, nurses, specialists, physicians, and others. According to Alonazi et al., the nurses have a significant role in perpetuating a healthy Saudi Arabia patient safety culture (14, 15). Although patient safety is the business of eve healthcare are practitioners, nurses have a key role to play in the entire process of providing quality healthcare services.

Investigating nurses' perspectives on patient safety is a critical step in enhancing the safety of patients in Saudi Arabia. However, as already mentioned, research studies by Eldeeb et al. and Khalil et al. reveal that many Saudi Arabia healthcare practitioners, including nurses, have reduced levels of patient safety (4, 11). Their low formal reporting on adverse events and the serial revisions of existing patient safety policies (16). In addition, policy modifications and compliance to existing processes (17) are only regarded seriously when an organization requests international accreditation, according to research by Akologo and colleagues.

In Saudi Arabia, the frequency at which nurse practitioners incidents of medical errors in hospitals is low. Therefore, in Saudi Arabia, communication obstacles in reporting such incidents remain high. The major impediment is the high risk of disciplinary measures when nurses confess to committing a patient safety violation (1, 13, 14, 18). If the Saudi Arabia patient safety culture is to improve significantly, feedback communication is a critical aspect that must be improved. Furthermore, nurses stated that in circumstances where the patient safety concern did not substantially impact patients, the percentage of error reporting remained high (9). As a

result of these findings, the tertiary healthcare system will be characterized by blame and anxiety, adversely harming the patient safety culture.

Research findings have repeatedly established the value of leadership in fostering a patient safety culture. In several studies (1, 17, 19, 20), pharmacists and nurses noted that support from leadership was critical in combating subsequent surgical and drug errors. Nurse and physician leaders, for instance, who admit the inevitability of mistakes show a positive attitude toward the problem as a system instead of seeing it as a mistake committed by an individual practitioner. Such leaders conduct detailed inquiries into the source of the error and take immediate action to address the core issues (19). Communication obstacles and fear of prosecution, for example, are cited as core reasons for significant patient safety issues by the management of numerous Saudi Arabia hospitals. As established by Alnasser et al., the Saudi Arabia healthcare industry is highly dominated by expatriates from non-Arabic speaking countries (3). As a result, there could be a communication problem between doctors and nurses, resulting in pharmaceutical errors being conveyed to hospitalized patients. Communication barriers may also prevent caregivers from fully comprehending medications, care plans, and follow-up treatment plans.

Various explanations have been highlighted in the literature as to why healthcare personnel has negative attitudes about patient safety culture. For example, the system has unfairly punished accused offenders of surgical and medication blunders (13, 15). The Ministry of Health has yet to adopt policies that examine the fundamental source of the problem and resolve it systematically. As a result, the rate of medical or surgical errors being reported is still quite low. Positive perceptions are connected with the frequency of errors and length of employment in places where medical and surgical mistakes are more commonly reported (1, 20, 21). Healthcare experts with extensive experience in the field report high rates of reporting incidences of errors. Moreover, healthcare institutions with a higher rate of patient safety issues appear to have more positive attitudes toward a culture of patient safety (1, 19, 21). Nevertheless, improving healthcare personnel's perceptions of patient safety requires more than just the rete of errors and experience.

Regrettably, medical research in Saudi Arabia lacks data on the extent of knowledge of issues affecting patient safety culture. Furthermore, it is uncertain what healthcare personnel expect regarding patient safety views (1, 22). Saudi Arabia currently has several policies in place to promote the establishment of a positive patient safety culture (1, 19). These policies, however, are seldom fully enforced, which explains why unfavorable impressions of patient safety persist. Based on this, the management of Saudi Arabia's healthcare facilities must demonstrate effective leadership to address all threats to the growth of patient safety. Specifically, they need to implement punitive measures against perpetrators of medical

errors. This way, their attitude toward patient safety will improve, consequently impacting the safety culture in the Saudi Arabia health care industry.

Research objectives

The main objective of this research is to assess the level of patient safety culture awareness among healthcare providers. Specific objectives of this study include identifying the main factors which hinder the implementation of patient safety, and determining demographic variables' effect on healthcare providers' awareness and perceptions of patient safety culture.

Materials and methods

Research strategy

The choice of the research strategy for this research is based on the research aim, objectives, and the existing research data and information on patient safety culture awareness among Saudi Arabia health care practitioners. Specifically, this research study applied a cross-sectional quantitative design. This is because it is the best research design method for measuring patient safety culture awareness among (healthcare providers. Additionally, since the researcher planned to select the participants using the inclusion and exclusion criteria, the cross-sectional quantitative design was the preferred research design strategy.

Research area/setting

This research was conducted in a tertiary hospital in Riyadh, Saudi Arabia.

Research participants

This research was based on the inclusion and exclusion criteria of the research participants. The inclusion criteria included healthcare workers in a tertiary hospital (Both clinical and non-clinical healthcare workers; participants' age was 20 years or above; the education level of participants a diploma or higher. The exclusion criteria included healthcare workers who do not work in a tertiary hospital; participants' age < 20 years; the education level of participants less than a diploma.

Research sample & sampling technique

Based on the aims and objectives of this research, the randomization sampling technique was applied. The researcher selected this sampling technique to eliminate biases by giving every individual in the research sample an equal opportunity to be a participant. After subjecting the research sample to inclusion and criteria, 409 participants were identified.

Data collection method, instruments used, measurements

The primary method of data collection for this research study was a valid and reliable questionnaire which was the Hospital Survey on Patient Safety Culture questionnaire. The questionnaire was anonymously distributed thru social networks to healthcare providers. All healthcare providers were briefed on the research aims and objectives beforehand.

The Hospital Survey on Patient Safety Culture questionnaire was adapted from the Agency for Healthcare Research and Quality (AHRQ) (22). The questionnaire elements were mildly modified to suit the researchers' intended respondents. The cultural sensitivity was also expertly evaluated.

The questionnaire was divided into two sections. The first section dealt with demographic information such as age, gender, years of experience, age, level of education, position in the hospital, and work area, while the other section included 12 aspects of patient safety culture. The 12 aspects covered in the second section include Patient Safety Rating, Communication Openness, Manager, Supervisor, Organizational Learning-Continued Improvement, Reporting Patient Safety Events, Number of Events Reported, Response to Error, Hospital Management Support for Patient Safety, Teamwork, Clinical Leader Support for Patient Safety, Hands-off and Information Exchange, Error Communication, and Staffing and Work Pace. The data for this study was collected *via* online platforms including social media networks.

Statistical analysis

The patient safety culture and the cumulative score were obtained by calculating the findings of the domain after flipping the negative concerns based on the research aims and objectives of the research study. Higher scores indicated a more patient-centered culture. All variables on the scale had their standard deviations and means calculated, followed by *T*-tests and ANOVA. *T*-test was used to explore the association between level of awareness and gender variable because it has two categories. While one-way analysis of variance (ANOVA) was used to explore the association between level of awareness and demographic variables such as age group and education level because they have more than two categories

The aim was to discover the significance among the means. The logistic regression was applied in checking the influence of

TABLE 1 Frequency and percentage of participants' characteristics.

Characteristic	Frequency	Percentage
Age		
20–30 years	27	6.6
31–40 years	247	60.4
41–50 years	111	27.1
More than 50 years	24	5.9
Gender		
Female	143	35.0
Male	266	65.0
Education		
Diploma	35	8.6
Bachelor's degree	266	65.0
Postgraduate	108	26.4
Position		
Medical	86	21.0
Nursing	64	15.6
Other Clinical Position	149	36.4
Supervisor, Clinical leader,	52	12.7
Senior leader, Manager, Executive		
Support services	58	14.2
Total	409	100.0

demographic variables on the level of awareness. The statistical significance level was set at 0.05.

Results

Descriptive statistics

The respondents of the study were 409 healthcare providers. Out of 409 respondents of the study, 6.6% were between the age of 20–30 years, 60.4% were between 31 and 40 years, 27.1% were between 41 and 50, and 5.9% were above the age of 50 years. As shown in Table 1, of the 409 participants, 143 (35%) were female, whereas 266 (65%) were male participants. Furthermore, Table 1 also contains statistics about the education status of the participants. The majority of the participants of the study (65%) had bachelor's degrees. Moreover, 21% had medical, 15.6% had nursing, whereas 36.4% had other clinical positions at the hospital.

Components of patient safety awareness culture (PSAC)

Table 2 shows the mean scores and standard deviation scores of different components of patient safety awareness culture were calculated. To measure the healthcare providers' beliefs about

the components, five points Likert scale was used (1, strongly disagree; 5, strongly agree) for the first seven components, whereas additional five points Likert scale (1, never; 5, always). Based on the mean score of 3.16, the value between 0.1 and 2.33 was considered a low level of awareness, the value between 2.34 and 3.66 was considered a moderate level of awareness, whereas the values above 3.66 were considered a high level of awareness. Staffing ($M = 3.66$) and communication about errors ($M = 3.46$) components had the highest mean scores. This means that healthcare providers' general staffing and their communication about errors were effective. On the other side response to error ($M = 2.67$) and hands-off and information exchange ($M = 2.76$) had the lowest mean scores. Overall, the mean score of patient safety awareness culture (PSAC) was 3.16. Thus, it can be concluded that there was a moderate level of patient safety awareness culture in the healthcare providers. Moreover, the mean scores of the other components of the scale, such as teamwork within units, organizational learning, management support for patient safety, communication openness, and reporting patient safety events, were reported as 3.04, 3.12, 3.20, 3.17, and 3.34, respectively.

One of the major purposes of the study was also to check whether there is any influence of gender on the level of patient safety culture awareness. The analysis revealed that the mean score of the female and male groups were 3.20 and 3.14, respectively. The 143 female participants ($M = 3.20$, SD = 0.24) compared to the 266 male participants ($M = 3.14$, SD = 0.23) demonstrated significantly better safety awareness. Moreover, the group's mean scores are statistically significant because the p-value is 0.009.

Moreover, a one-way analysis of variance (ANOVA) was used to compare the variance in the group means within a sample. Age Group, level of education, position in the hospital, and work area variables were used as factors, whereas patient safety awareness culture (PSAC) was used as the dependent variable. The findings revealed in Table 3 that there is a statistically significant difference between the age groups as determined by one-way ANOVA (p-vale = 0.020). Similarly, a statistically significant difference was identified between the groups of the level of education p-value = 0.008). Whereas the results found no significant between means in position in the hospital and the same result was found in the work area domain.

As ANOVA test confirmed that the overall results were significant. Moreover, Tukey's Honest Significant Difference test was run to identify which group means are significantly different from another group's means. Tables 4, 5 show the multiple comparison analysis of the variable of age and education level. As the Tukey *post-hoc* test shows in Table 4, the 31–40 years age group showed statistically different awareness levels as compared to the "more than 50 years age group" ($p = 0.012$). The results of the Tukey *post-hoc* test in Table 5 show that the participants having diplomas showed statistically different

TABLE 2 Mean and Std. Deviation of Domains of PSA.

Domains	Mean	±SD	Level of Awareness
Staffing	3.66	0.59	Moderate
Teamwork within units	3.04	0.45	Moderate
Organizational learning	3.12	0.53	Moderate
Response to errors	2.67	0.47	Moderate
Management support for patients' safety	3.20	0.55	Moderate
Hospital management support for patient safety	3.19	0.57	Moderate
Hands off and information exchange	2.76	0.56	Moderate
Communication about errors	3.46	0.66	Moderate
Communication openness	3.17	0.61	Moderate
Reporting patient safety events	3.34	0.80	Moderate
All Domains	3.16	0.23	Moderate

TABLE 3 ANOVA table for the demographic data on the level of awareness.

Variables	Source	Sum of squares	Degree of freedom	Mean Square	Sig.
Age Group	Between Groups	0.526	3	0.175	0.020
	Within Groups	21.42	405	0.053	
Level of Education	Between Groups	0.521	2	0.261	0.008
	Within Groups	21.429	406	0.053	

awareness levels as compared to the participants having a bachelor's degree ($p = 0.006$).

Discussion

This study is regarding patient safety culture awareness among health care practitioners based on current research and information. This study uncovered a few key findings on healthcare providers' perceptions and demonstrations the level of awareness of patient safety culture. This is because, while such findings are limited, they can provide significant data and information to the Saudi Arabia healthcare business and hospital administration about how to improve the level of patient safety culture among healthcare professionals for better patient care.

After calculating the mean scores and standard deviation scores of different components of patient awareness culture, it was discovered that there was a moderate level of patient safety awareness culture among healthcare providers. For all the components considered, all the means fell between 2.67 and 3.66, which was considered as a moderate level of awareness (2.34–3.66). Alshammari et al. did a research investigation that backs up the conclusions of this study. Alshammari et al. used a descriptive cross-sectional technique to assess the perspectives of healthcare practitioners about the culture of patient safety in their study (13). The study was carried out at four large Saudi Arabia hospitals.

According to the findings of their research, the practice of patient safety is widely accepted among Saudi Arabia healthcare providers. They found positive relationships between study participants' profiles and patient safety dimensions. Furthermore, Aboshaiqah and colleagues discovered that nurses in Saudi Arabia had a positive opinion of patient safety culture in a survey targeted at finding out what they thought about it (23). According to the findings of this study, most healthcare professionals are aware of the necessity of patient safety culture, even if it has not yet been established in the system.

The findings also found that healthcare workers' general staffing and error communication is successful. Griffiths et al. found a link between nursing staffing and a number of patient safety outcomes in their investigation (24). Jahan and Siqiqqui also established that the doctor-patient relationship has a significant impact on health outcomes (25). For any relationship to thrive, communication is an essential component, particularly between a health practitioner and a patient. The author noted that in healthcare settings, communication is thorough and strong. Patient consistency and contentment improve with good communication. A physician's moral obligation is to answer all of the patient's questions and to make therapy and its effects as simple as possible. In line with the above studies, our study reveals that healthcare professionals in Saudi Arabia are aware of the importance of staffing and communication in promoting a culture of patient safety.

TABLE 4 Multiple Comparison Analysis (*post-hoc*-Tukey HSD of Age Group).

(I) Age	(J) Age	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence	
					Lower Bound	Upper Bound
31–40 years	20–30 years	0.04	0.04	0.798	−0.077	0.162
	41–50 years	0.02	0.02	0.785	−0.043	0.092
	More than 50 years	0.15*	0.04	0.012	0.024	0.278

*The mean difference is significant at level ≤ 0.05.

TABLE 5 Multiple Comparison Analysis (*post-hoc*-Tukey HSD of Education Level).

(I) Education level	(J) Education level	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence	
					Lower Bound	Upper Bound
Bachelor's degree	Diploma	0.12*	0.041	0.006	0.029	0.224
	Postgraduate	0.03	0.026	0.455	−0.030	0.093

*The mean difference is significant at level ≤ 0.05.

Although the research has established that healthcare practitioners in a tertiary hospital have a high mean of communication about errors (3.46), it contradicts the finding that they have a low mean of response to errors (2.67). This is because it is absurd for a healthcare practitioner to identify and communicate about a medical error and not respond to it on time. Nevertheless, this research finding regarding response to errors supports the finding by Alsafi et al., who earlier established a decrease in error reporting (49%) among Saudi Arabia healthcare providers. According to Alsafi et al., 49 percent of Saudi Arabia healthcare providers do not report formally medical errors if they (the errors) do not harm them (26). In terms of reporting patient safety events, the tertiary hospital has a high level of awareness (3.34). This is attributed to many factors, such as constant departmental training on the same and excellent patient counseling.

This research has found that hospital management supports patient safety culture (3.19). This, as already mentioned, could be due to constant staff training organized by hospital leaders. Globally, lack of hospital support has cost the healthcare industry approximately 42$ billion (3). The finding on the management of the tertiary hospital support for patient safety contradicts the findings by Alsulami and his colleagues, who established that approximately 44% of healthcare providers in Saudi Arabia tertiary healthcare setups do not understand the meaning of patient safety (27). This implies that the hospital's administrational support for patient safety is "a continuum of the healthcare system" (27). There are other reasons to explain why the management at the tertiary hospital has high support for patient safety. Research by Wittich et al. (31) attributes it to various factors, including a high therapeutic index (28). Additionally, Alsafi et al. observe that it could be attributed to the knowledge of various patient factors, including

poor hepatic or renal function, polypharmacy, and impaired cognition (26). Alsafi et al. also acknowledge factors related to healthcare practitioners.

Demographic variables such as gender, age, education, hospital position, and work location had a low to moderate impact on the level of patient safety culture awareness among healthcare personnel, according to the findings of this study. There was a statistically significant difference between the age groups, according to the findings. It, therefore, means that age is a component of this study, affecting how healthcare practitioners perceive patient safety culture in Saudi Arabia. A research study by Jabarkhil et al. attributes this to their ability to handle strenuous workloads, workplace stress, and depression more easily (27). We can conclude that for the age category "31–40 years," for every addition of a year, the awareness level increases. Similarly, for the age category "41–50 years," the awareness level increases significantly. However, the category "More than 50 years" is taken as a reference category, and all other age categories are compared with it. According to Jabarkhil, this age categorization is prone to old age diseases such as mental loss (27). Coupled with workplace workloads, stress, and depression, they may not be able to recognize the violation of the expected patient safety protocols.

Another demographic component examined in the study is the influence of gender on the level of patient safety culture awareness. The findings show that the level of patient safety culture awareness among healthcare providers is strongly influenced by the age of the healthcare providers. Since the *P*-value was <0.05 (level of significance), the group's mean scores were statistically significant. Females demonstrated a significantly better safety awareness as compared to males. This could be attributed to the caring nature of females, which makes them more sensitive to patient safety than their male counterparts. Gender significantly directly affects

both managerial and professional functions (29). The research findings further show that for different employee positions within the tertiary hospital, various PSAC aspects do not significantly relate to their General Patient Safety Perception. The position does not influence the "patient safety culture" awareness among healthcare providers.

In terms of the level of education, the participants having diplomas showed statistically different awareness levels as compared to the participants having a bachelor's degree ($p = 0.006$). It indicates that diploma courses in Saudi Arabia give more attention to patient safety practices as compared to bachelor's degrees and postgraduate. Negligence could originate from an assumption that since the students are at a higher level of learning, they need to be taught more advanced concepts.

According to the 2021 report by the World Health Organization, the organization is committed to providing useful information on medication safety, polypharmacy, high-risk situations, and transitional care (29). However, relevant research applicable for Saudi Arabia healthcare providers is lacking. In research conducted by Alenezi and his colleagues aiming to evaluate the perception of healthcare providers in accordance with their facility's "patient safety culture," it was established that hospitals need to strengthen to enhance patient safety culture (30). For improving patient safety culture, Hospital managers need to focus on improving factors such as conducting training programs to reduce human-related incidents; enhancing safety monitoring and measuring system; Learning from the successful experience of other hospitals; Digitalization of healthcare management; Keeping patients informed to monitor their own treatment; improving communication among healthcare providers; focusing on hand hygiene procedure.

Limitation

This research was conducted in one tertiary healthcare organization in Saudi Arabia. For this reason, the findings here are not entirely applicable to the whole Saudi Arabia healthcare industry. In addition, distributing the data collection tool was done *via* social networks or online platforms which means the healthcare providers who are not active in social networks did not get enough chance to participate in this study.

Conclusion

The findings of this study revealed that healthcare providers have a modest level of "patient safety culture" awareness.

Moreover, the findings also revealed that gender and education have a significant influence on the awareness level of "patient safety culture" among health care practitioners. On the other hand, position and work area have no influence on the level of "patient safety culture" awareness among healthcare providers. The results, therefore, affirm the first hypothesis that there is a moderate level of "patient safety culture" awareness among healthcare providers.

Moreover, the age of healthcare providers in the tertiary hospital has a statistically significant influence on the level of "patient safety" culture awareness. Specifically, this research has established that healthcare providers within the age of 31–40 are aware of the importance of patient safety culture ($p = 0.001$). This may be attributed to their ability to handle strenuous workloads, workplace stress, and depression more easily. Thus, this study has established that the age of the healthcare providers significantly influences the level of "patient safety culture" awareness among healthcare providers.

Based on the results of this study, there are several recommendations for action have been developed. Healthcare institutions should develop speeder response plans and make them part of the patient safety culture. Institutions offering Bachelor's degrees and postgraduate in nursing should pay more attention to the subject of patient safety. The Healthcare wing of the government, together with healthcare institutions, should continuously train healthcare professionals on the importance of "patient safety culture" and the various ways of responding to alarms. Health professionals should be encouraged to report errors made during diagnosis or treatments to improve patient safety.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Centre, Riyadh, Saudi Arabia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

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Conflict of interest

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

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Assessing Canadian women's preferences for cervical cancer screening: A brief report

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Human papillomavirus (HPV) testing is recommended for primary screening
for cervical cancer by several health authorities. Several countries that have
implemented HPV testing programs have encountered resistance against
extended screening intervals and older age of initiation. As Canada prepares
to implement HPV testing programs, it is important to understand women's
preferences toward cervical cancer screening to ensure a smooth transition.
The objective of this study was to assess Canadian women's current
preferences toward cervical cancer screening. Using a web-based survey,
we recruited underscreened (> 3 years since last Pap test) and adequately
screened (< 3 years since last Pap test) Canadian women aged 21–70 who
were biologically female and had a cervix. We used Best-Worst Scaling
(BWS) methodology to collect data on women's preferences for different
screening methods, screening intervals, and ages of initiation. We used
conditional logistic regression to estimate preferences in both subgroups.
In both subgroups, women preferred screening every three years compared
to every five or ten years, and initiating screening at age 21 compared to
age 25 or 30. Adequately screened women ($n = 503$) most preferred co-
testing, while underscreened women ($n = 524$) preferred both co-testing and
HPV self-sampling over Pap testing. Regardless of screening status, women
preferred shorter screening intervals, an earlier age of initiation, and co-testing.
Adequate communication from public health authorities is needed to explain
the extended screening intervals and age of initiation to prevent resistance
against these changes to cervical cancer screening.

KEYWORDS

human papillomavirus, cervical cancer screening, cancer prevention, Best-Worst
Scaling, HPV test, cytology, women's preferences for cervical cancer screening

Introduction

Cervical cancer presents a threat to women's health and the health of all individuals with a cervix. In Canada, each year, approximately 1,300 women are diagnosed with cervical cancer and about 400 die (1). In the last decade, recommendations from multiple health authorities have been updated to include Human Papillomavirus (HPV) testing for primary screening for cervical cancer (2–4). Notably, the World Health Organization (WHO) now recommends HPV testing as the primary method of cervical cancer screening globally (5). Strong evidence exists that HPV testing provides significantly greater protection against invasive cervical carcinomas compared with cytology (Pap test) and earlier detection of cervical pre-cancers (6–8). While recommendations for cytology-based screening typically include a 3-year interval between negative tests, HPV-based screening is recommended at a 5-year interval, considering the test's high negative predictive value (2, 9, 10). Moreover, in countries that have transitioned from cytology-based to HPV-based primary screening programs, the age of screening initiation has changed from 21 to 25 years (Australia, the UK) (4) or 30 years (the Netherlands) (11) considering both the limited evidence of benefit in screening younger women and the harms of over-screening that lead to overtreatment of cervical lesions and subsequent adverse reproductive outcomes (12, 13). The Canadian Partnership Against Cancer Action Plan's goals for elimination of cervical cancer include screening 90% of eligible women with an HPV test (14). Currently, most provinces are preparing to include HPV-testing as the primary approach (including self-sampling, the option of self-collecting vaginal samples for HPV testing) in cervical cancer screening programs.

Important challenges in transitioning from cytology to HPV-based primary screening are due to women's and healthcare professionals' hesitancy to accept longer screening intervals and postpone screening initiation beyond 21 years (15, 16). Implementation experience from Australia and Wales indicate that women have anxieties and concerns about moving to longer screening intervals (every 5 years) and a later initiation of cervical cancer screening (25 years old) which resulted in up to 1.2 million women signing online petitions against the transition toward HPV testing (17, 18). In Canada, findings from the HPV FOCAL trial in British Columbia have presented evidence related to women's acceptance of longer intervals with HPV-based screening and later screening initiation beyond 21 years (19, 20). The HPV FOCAL trial was a 48-month randomized controlled trial comparing the incidence of cervical intraepithelial neoplasia (grade 2 or greater) in participants who received HPV testing for cervical screening vs. cytology. At the 48-month study exit, all participants received co-testing (HPV and cytology) allowing for assessment of acceptance of HPV testing. Given the HPV FOCAL cohort received education about and experience with HPV testing, their preferences toward cervical cancer screening may not be reflective of the Canadian population's baseline attitudes.

As most Canadian women have not yet had experience with HPV testing to date, it is important to understand women's current preferences for cervical cancer screening modalities (cytology vs. HPV testing), age of screening initiation (beyond age 21), and longer screening intervals (5 years or more after a negative HPV test) to inform future implementation strategies. Achieving optimal screening uptake in the context of transitioning from cytology to HPV test-based screening could be complicated by low acceptability for the change among women who are accustomed to existing screening recommendations (21, 22). Additionally, there is a need to examine and address existing barriers to screening amongst vulnerable women (e.g., lower socioeconomic status, recent immigrants) (23, 24). The objective of the study is to assess Canadian women's current preferences for cervical cancer screening in order to develop appropriate communication and education strategies about HPV testing for both currently underscreened and adequately screened women.

Methods

Study design and participants

In the present study, we used a cross-sectional design to collect data from Canadian women using a web-based survey in October/November 2021. The study was conducted as part of a larger project funded by the Canadian Institutes of Health Research estimating psychosocial correlates of women's intentions to participate in HPV-based primary screening to prevent cervical cancer. Women answered questions about the following topics: their screening history and health; knowledge of cervical cancer screening; knowledge of HPV testing; attitudes and beliefs toward HPV testing; attitudes and beliefs toward HPV-based self-sampling; and preferences for cervical cancer screening options. Several specific informative statements were provided at different points of the survey to give participants basic information before responding to each section. One informative statement introduced that HPV was the primary cause of cervical cancer, and that HPV testing could allow longer intervals between cervical cancer screenings: "Research shows that if HPV DNA is not found, women are at very low risk for cervical cancer and do not need to screen for cervical cancer as often as with the Pap test (e.g., every 5 years)". All informative statements are available in Appendix A. Full details of the overall study design and all measures used are available elsewhere, (25).

Participants who met the following criteria were enrolled in the study: (1) Canadian resident; (2) biologically female; (3) between the ages of 21–70; and (4) having a cervix (e.g., never undergone a hysterectomy). The exclusion criterion was having been previously diagnosed with cervical cancer.

Data collection was facilitated by Dynata, and international survey company. Dynata uses a combination of email, website, and in-app invitations to invite participants to complete a survey on "Health and Wellness." Recruitment included census-based quotas for primary language (English/French) and province of residence to ensure sample representativeness. Oversampling was used to ensure half of the participants were underscreened for cervical cancer (i.e., longer than three years since previous Pap test or never screened). Participants responded to the survey in either English or French. Ethics approval was obtained from the Research Ethics Board of the CIUSSS West-Central Montreal (Project ID: 2021–2632).

Variables

Socio-demographic variables included both continuous (age) and categorical variables. Some variables were recategorized due to small cell counts. Gender was measured using validated categories that capture socially constructed roles, identities, and behaviors (26), and two categories were retained for analysis: female, and other. Household income was measured in $10,000 increments. Self-reported ethnicity was measured using the nine categories recommended by Statistics Canada (27), and was recategorized into North American Aboriginal, Other North American, European, Asian, and Other (i.e., Caribbean, Latin, Central and South American, African, dual/mixed ethnicities, and uninterpretable open-ended responses). Province or territory was recategorized into Western, Central, and Eastern Canada. Marital status was measured using three categories: married/common-law, single, and dating but do not live with partner. Language spoken at home was measured using three categories: English, French, and other. Dichotomous (yes/no) socio-demographic items included: identification as a visible minority; influence of religious or spiritual beliefs on health decisions; living in Canada for 10 years or more; and completion of a trade certificate/diploma, college or CEGEP degree, or University degree.

Cervical cancer screening history was assessed using the following item: "*When did you have your last Pap test? Select the option that best describes you.*" Response options included: (a) *I had a Pap test within the last year*; (b) *I had a Pap test within the last 1 to 3 years*; (c) *I had a Pap test over 3 years ago*; (d) *I have never had a Pap test*. Participants answering "a" or "b" were categorized as "adequately screened" and those answering "c" or "d" were categorized as "underscreened."

Unlike traditional methods of assessing preferences (e.g., multiple choice questions), Best-Worst Scaling (BWS) methodology allows for the in-depth assessment of preferences by asking participants to consider the trade-offs of selecting certain combinations of attributes and attribute levels over others through a series of questions that contain a random

combination of attribute-levels. We used case 2 BWS methodology (28) for measuring preferences for screening intervals (Domain A) and age of screening initiation (Domain B). Both domains shared the same four attributes (screening methods), which were: Pap test; HPV test; both the Pap test and the HPV test (herein, "co-testing"); and HPV test using self-sampling. For each attribute, we selected three attribute-levels (i.e., screening interval options for Domain A, i.e., every 3 years, every 5 years, every 10 years) and three attribute-levels reflecting age of initiation options for Domain B (i.e., 21 years old, 25 years old, 30 years old). The attribute-levels were chosen based on current cervical cancer screening recommendations or programs in Canada, as well as in other countries where HPV testing has already been implemented (2, 29–31). For each of the two domains, participants answered nine questions, for a total of 18 questions. The order of questions within a domain and the order of the domains were randomized to minimize response bias. To generate questions we used the orthogonal main effect design methodology recommended by Aizaki (32) and the R software packages "DoE.base" (33) and "support.BWS2" (32). See Appendix B for Domain A and Domain B questions.

Statistical analysis

To identify careless responders, we incorporated two attention check questions in the survey. Participants were instructed to select a specific response choice from a Likert scale (e.g., Please select "strongly agree," for this question only). Those who responded incorrectly to both attention check questions were excluded from subsequent analyses. Straightliners (i.e., those who responded to all items with the same answer) were identified by calculating their response variance to one of the sections of the survey (the HPV testing attitudes and beliefs items) (34), and excluded. Participants who were in the longest 2.5% and shortest 2.5% survey response times were also excluded.

For reporting descriptive socio-demographics, we calculated proportions, means (and standard deviations, SD), and used Pearson's Chi-Square test and T-tests to determine whether adequately screened and underscreened women differed significantly. We reported effect sizes using Cohen's d for T-tests, and Cramer's V for Pearson's Chi-Square test. We interpreted V = 0.1 as a small effect, V = 0.3 as a medium effect, and V = 0.5 as a large effect (35). BWS data was analyzed using the counting and the modeling approaches described by Aizaki and Fogarty (2019) (28). Corresponding to the counting approach, within each domain we calculated the best-minus-worst (BW) total score for each attribute and attribute level and used the function "bws2.count" from the package "support.BWS2" in R. Further, we used conditional logistic regression to estimate preferences and the marginal model that is based on the assumption that respondents
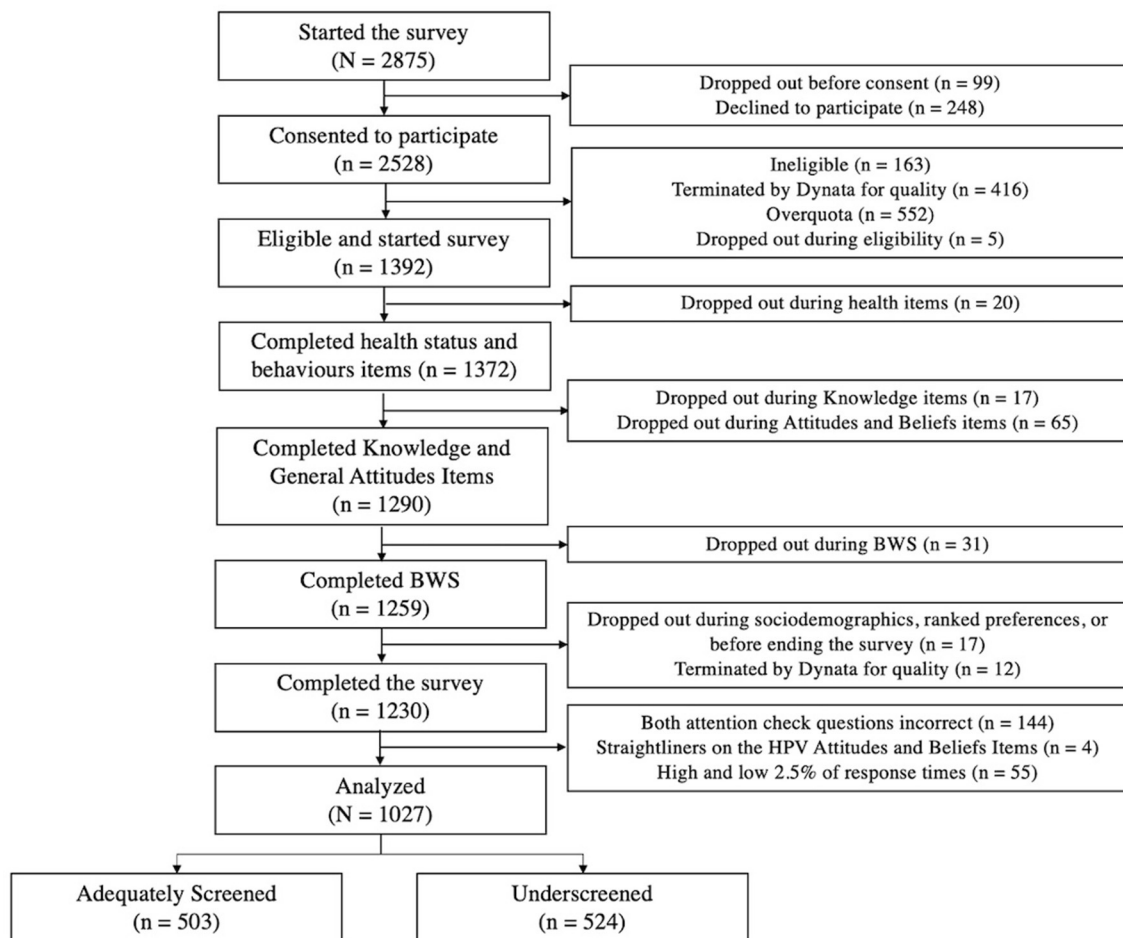
FIGURE 1
Participant flow.

evaluated all attribute-levels both when choosing the best and the worst attribute-level in each question (28). In each model (corresponding to Domain A and B), one attribute and one attribute-level (per attribute) were omitted from the utility function and treated as reference categories. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using the "clogit" function and the "survival" package in R (36).

Results

A total of 1,230 participants completed the survey. Careless responders ($n = 203$) were identified and excluded from subsequent analyses. The final sample used for analyses consisted of 1,027 participants with $n = 503$ adequately screened and $n = 524$ underscreened (See Figure 1).

The sample consisted of mostly females (99.6%); the mean age was 48.4 years old; most spoke English at home (74.5%); most have lived in Canada for 10 years (96.4%); most had

post-secondary education (69.9%); and most were married (59.5%). The following socio-demographic variables differed significantly between those who were adequately screened and those who were underscreened, although all effect sizes were small: ethnicity ($\chi^2 = 11.03$, $p = 0.03$, V = 0.10); self-perceived visible minority ($\chi^2 = 10.65$, $p < 0.001$, V = 0.10); language spoken at home ($\chi^2 = 8.13$, $p = 0.02$, V = 0.09); marital status ($\chi^2 = 14.88$, $p < 0.001$, V = 0.12); household income ($\chi^2 = 30.48$, $p < 0.001$, V = 0.17); and Canadian region ($\chi^2 = 11.36$, $p < 0.001$, V = 0.11) (See Table 1).

Preferences for screening methods and cervical cancer screening intervals

The analysis of preference for screening methods (attributes) shows that both adequately screened ($_{adq}$) and underscreened women ($_{und}$) preferred co-testing (BWs $_{adq}$ = 977; BWs $_{und}$

TABLE 1 Socio-demographic variables.

	Total $n = 1027$	Adequately screened $n = 503$	Underscreened $n = 524$	Between group difference	Effect size
	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)		
Age	48.4 (12.6)	48.8 (12.0)	47.9 (13.1)	$p = 0.28$	$d = 0.01$
Gender					
Female	1023 (99.6)	501 (99.6)	522 (99.6)	$\chi^2 = 0.00\ p = 0.97$	$V = 0.00$
Other	4 (0.4)	2 (0.4)	2 (0.4)		
Ethnicity					
North American Aboriginal	30 (2.9)	17 (3.4)	13 (2.5)	$\chi^2 = 11.03\ p = 0.03^*$	$V = 0.10$
Other North American	462 (45.0)	232 (46.1)	230 (43.9)		
European	340 (33.1)	176 (35.0)	164 (31.3)		
Asian	145 (14.1)	53 (10.5)	92 (17.6)		
Other	50 (4.9)	25 (5.0)	25 (4.8)		
Self-perceived visible minority					
Yes	198 (19.0)	75 (14.9)	120 (22.9)	$\chi^2 = 10.65\ p < 0.001^*$	$V = 0.10$
No	832 (81.0)	428 (85.1)	404 (77.1)		
Influence of religion on health decisions					
Yes	112 (10.9)	45 (8.9)	67 (12.8)	$\chi^2 = 3.90\ p = 0.05$	$V = 0.06$
No	915 (89.1)	458 (91.1)	457 (87.2)		
Language spoken at home					
English	765 (74.5)	394 (78.3)	371 (70.8)	$\chi^2 = 8.13\ p = 0.02^*$	$V = 0.09$
French	211 (20.5)	90 (17.9)	121 (23.1)		
Other	51 (5.0)	19 (3.8)	32 (6.1)		
Living in Canada for 10 years					
Yes	990 (96.4)	490 (97.4)	500 (95.4)	$\chi^2 = 2.94\ p = 0.09$	$V = 0.05$
No	37 (3.6)	13 (2.6)	24 (4.6)		
Education (any post-secondary)					
Yes	718 (69.9)	359 (71.4)	359 (68.5)	$\chi^2 = 1.00\ p = 0.32$	$V = 0.03$
No	309 (30.1)	144 (28.6)	165 (31.5)		
Marital status					
Married/common-law	611 (59.5)	326 (64.8)	285 (54.4)	$\chi^2 = 14.88\ p < 0.001^*$	$V = 0.12$
Single	377 (36.7)	155 (30.8)	222 (42.2)		
Dating but do not live with partner	39 (3.8)	22 (4.4)	17 (3.2)		
Household income in 2019 before the COVID-19 pandemic (CAD)					
< 40,000	260 (25.3)	91 (18.1)	169 (32.3)	$\chi^2 = 30.48\ p < 0.001^*$	$V = 0.17$
40,000–79,999	354 (34.5)	179 (35.6)	175 (33.4)		
> 80,000	394 (38.4)	224 (44.5)	170 (32.4)		
Prefer not to answer	19 (1.9)	9 (1.8)	10 (1.9)		
Canadian region					
Western	314 (30.6)	157 (31.2)	157 (30.0)	$\chi^2 = 11.36\ p < 0.001^*$	$V = 0.11$
Central	652 (63.5)	304 (60.4)	348 (66.4)		
Eastern	61 (5.9)	42 (8.3)	19 (3.6)		

*Indicates a significant difference between adequately screened and underscreened groups.

= 418) or the HPV test (BWs $_{adq}$ = −224; BWs $_{und}$ = −397) compared to the Pap test (BWs $_{adq}$ = −333; BWs $_{und}$ = −522). We found 100% and 51% higher odds of preference for co-testing vs. Pap in adequately and underscreened participants respectively. Importantly, among adequately screened women self-sampling was the least preferred screening method (BWs = −420) while in underscreened women, self-sampling was the most preferred screening method (BWs = 501) (See Table 2).

TABLE 2 Preferences for screening intervals (Domain A).

Attributes	Whole sample (n = 1027)		Adequately screened (n = 503)		Underscreened (n = 524)	
	BWs	OR (95% CI)	BWs	OR (95% CI)	BWs	OR (95% CI)
Pap Test	−855	ref	−333	ref	−522	ref
HPV Test	−621	1.06 (1.01; 1.10)	−224	1.06 (1.00; 1.13)	−397	1.06 (1.00; 1.12)
Pap and HPV test	1395	1.69 (1.62; 1.76)	977	2.00 (1.88; 2.14)	418	1.51 (1.43; 1.60)
HPV Self–Sampling	81	1.23 (1.17; 1.28)	−420	0.91 (0.85; 0.97)	501	1.56 (1.48; 1.66)
Levels for attribute: Pap test						
Every 3 years	305	1.75 (1.66; 1.84)	369	2.71 (2.51; 2.92)	−64	1.22 (1.14; 1.30)
Every 5 years	−108	ref	−44	ref	−64	ref
Every 10 years	−1052	0.49 (0.46; 0.51)	−658	0.31 (0.29; 0.33)	−394	0.68 (0.64; 0.73)
Levels for attribute: HPV test						
Every 3 years	341	1.65 (1.57; 1.73)	331	2.26 (2.10; 2.44)	10	1.28 (1.19; 1.36)
Every 5 years	−115	ref	−55	ref	−60	ref
Every 10 years	−847	0.54 (0.52; 0.57)	−500	0.39 (0.36; 0.42)	−347	0.69 (0.64; 0.73)
Levels for attribute: Pap and HPV test						
Every 3 years	1289	2.14 (2.03; 2.25)	948	3.64 (3.36; 3.94)	341	1.42 (1.33; 1.52)
Every 5 years	756	ref	443	ref	313	ref
Every 10 years	−650	0.36 (0.34; 0.38)	−414	0.22 (0.20; 0.24)	−236	0.52 (0.49; 0.56)
Levels for attribute: HPV self–sampling						
Every 3 years	585	1.68 (1.60; 1.77)	216	2.14(1.99; 2.31)	369	1.42 (1.33; 1.52)
Every 5 years	243	ref	−44	ref	287	ref
Every 10 years	−747	0.48 (0.46; 0.50)	−592	0.37 (0.35; 0.40)	−155	0.57 (0.53; 0.61)

Pertaining to screening intervals (attribute levels), for all screening methods and independent of screening status, women preferred most a 3-year interval followed by a 5-year interval and a 10-year interval between tests. For example, in adequately screened women we found BWs = 948; BWs = 443; and BWs = −414 for screening with both the Pap and HPV test every three; five; and ten years respectively. In both subgroups and for all screening methods, we found significantly higher preferences for screening every 3 years compared to 5 years and lower preferences for screening every 10 years vs. 5 years, e.g., in adequately screened women, OR = 3.64 (CI: 3.36; 3.94) and OR= 0.22 (CI = 0.20; 0.24) respectively (See Table 2).

Preferences for screening methods and age of initiation for cervical cancer screening

In domain B, the most preferred screening method (attributes) in both subgroups was co-testing (BWS $_{adq}$ = 1207; BWs $_{und}$ = 508) and preferences were significantly higher compared to the Pap test (OR $_{adq}$ = 2.20; CI: 2.06; 2.35; OR $_{und}$ = 1.59; CI: 1.50; 1.69). As with the results for domain A (screening intervals) the least preferred screening method in

adequately screened women was self-sampling (BWs= −693) and preferences were 20% lower compared to Pap (OR= 0.80; CI: 0.75; 0.85). In underscreened women, self-sampling was the second most preferred option (BWs= 378) after co-testing and preferences were significantly higher for self-sampling compared to Pap (OR = 1.50; CI: 1.41; 1.59) (See Table 3).

For all screening methods and independent of screening status, women preferred screening initiation (attribute levels) at age 21, followed by 25, and 30. With the exception of screening with HPV testing starting at 25 years in adequately screened women (where the result was not statistically significant [OR = 1.06; CI: 0.98; 1.14]), independent of the screening method, preferences were significantly higher for screening initiation at age 21 or 25 compared to 30 years (See Table 3).

Discussion

Using BWS methodology, this study aimed to understand Canadian women's current preferences toward cervical cancer screening intervals, ages of screening initiation, and screening methods.

We found that the three-year screening option was most preferred by women regardless of screening status and this aligns with findings from women in the HPV FOCAL trial

TABLE 3 Preferences for age of screening initiation (Domain B).

Attributes	Whole sample ($n = 1027$)		Adequately screened ($n = 503$)		Underscreened ($n = 524$)	
	BWs	OR (95% CI)	BWs	OR (95% CI)	BWs	OR (95% CI)
Pap Test	−870	ref	−320	ref	−550	ref
HPV Test	−530	1.08 (1.04; 1.13)	−194	1.06 (1.00; 1.13)	−336	1.10 (1.04; 1.16)
Pap and HPV test	1715	1.82 (1.74; 1.90)	1207	2.20 (2.06; 2.35)	508	1.59 (1.50; 1.69)
HPV Self–Sampling	−315	1.12 (1.08; 1.17)	−693	0.80 (0.75; 0.85)	378	1.50 (1.41; 1.59)
Levels for attribute: Pap test						
21 years old	296	1.73 (1.65; 1.82)	305	2.33 (2.16; 2.50)	−9	1.36 (1.27; 1.46)
25 years old	−214	ref	−94	ref	−120	ref
30 years old	−952	0.54 (0.51; 0.56)	−531	0.41 (0.38; 0.44)	−421	0.66 (0.62; 0.71)
Levels for attribute: HPV test						
21 years old	421	1.72 (1.64; 1.81)	354	2.31 (2.14; 2.48)	67	1.36 (1.27; 1.46)
25 years old	−131	1.07 (1.01; 1.12)	−69	1.06 (0.98; 1.14)	−62	1.10 (1.03; 1.17)
30 years old	−820	ref	−479	ref	−341	ref
Levels for attribute: Pap and HPV test						
21 years old	1372	2.09 (1.99; 2.20)	961	3.17 (2.93; 3.43)	411	1.52 (1.42; 1.63)
25 years old	777	1.20 (1.14; 1.26)	497	1.19 (1.10; 1.28)	280	1.21 (1.13; 1.29)
30 years old	−434	ref	−251	ref	−183	ref
Levels for attribute: HPV self–sampling						
21 years old	387	1.58 (1.50; 1.66)	94	1.98 (1.84; 2.13)	293	1.34 (1.25; 1.43)
25 years old	37	1.15 (1.10; 1.21)	−158	1.17 (1.09; 1.26)	195	1.13 (1.06; 1.21)
30 years old	−739	ref	−629	ref	−110	ref

where acceptance of extending screening intervals to 4–5 years was found to be lower than expected (54%), especially as participants received educational content about these changes (19, 20). This has been identified as a common concern for women in other countries where screening programs have extended screening intervals in the context of the implementation of HPV-based primary screening. For instance, several studies in Australia and England suggest that many women believe that longer intervals could result in delayed detection and treatment of cervical cancer (21, 37–39). Our results strongly suggest that extending screening intervals beyond the current 3-year practices will be of concern to Canadian women. When Canadian provinces introduce HPV-based screening with extended screening intervals, specific educational content addressing reasons for and reassuring women about the safety and appropriateness of these extended intervals will be essential to ensure broad acceptance. Waller et al. (40) demonstrated that providing messages about HPV test accuracy, safety, and explaining the speed of cell change in cervical cancer development resulted in more positive attitudes toward extending screening intervals to 5 years. Although two or three-year intervals are currently implemented in Canada (41), some healthcare providers recommend screening more often (15), which may further

reinforce resistance to screening intervals being extended beyond 3 years.

Regarding age of initiation, we found that both adequately screened and underscreened women significantly preferred 21 years and 25 years for screening initiation, in contrast to the findings of Smith et al. (19) who found that 69% of women accepted commencing screening with the HPV test at 30 years (19). Importantly, participants in the FOCAL trial were provided education about and experience with HPV based screening, whereas our study participants only received minimal information to complete the survey. Therefore, differences in acceptance likely emanate from the differences in education and highlight the need for large-scale efforts on a population level to educate women about these changes. Additionally, as using BWS methodology allows us to understand women's preferences while considering other alternatives, our findings might suggest that women are less likely to endorse later screening initiation when comparing it to earlier screening ages than examining it in isolation. Public health authorities should consider such trade-offs women face with these policy changes when planning the implementation and communication of changes. For example, a study of Australian women aged 18–24 who are no longer recommended for cervical cancer screening found that those who had previously received a Pap test felt

less positive about the extended age of initiation than those who had never received a Pap test, suggesting a need to specifically consider the concerns of women directly impacted by policy changes (42). Importantly, results of qualitative studies align with our results as they have highlighted concern from women about younger women being at risk of developing cervical cancer when considering screening initiation beginning at age 25 (21, 37, 38).

Our results showed that adequately screened women preferred to be screened with co-testing or the HPV test compared to the Pap test, while underscreened women preferred HPV self-sampling or co-testing. The contrast in the preferred methods between adequately and underscreened women indicates that offering them different sample collection methods (something that cytology-based screening does not currently allow) may increase uptake of cervical cancer screening, especially amongst underscreened women. As suggested by Vahabi & Lofters. (18, 43), offering HPV self-sampling, which underscreened women significantly preferred over the Pap test in our study, could be an effective method of screening to reach this population in Canada. In Canada, studies have found that difficulties with scheduling an appointment, inconvenient clinic hours, lack of time, and social stigma associated with screening to be barriers faced by underscreened women (23, 44). Studies from Australia and New Zealand, among others, have found that offering HPV self-sampling can increase screening participation amongst underscreened women (45–47), and our findings indicate that its use would be worth exploring in Canada as well.

Limitations and implications

Our study provides an initial signal that without adequate education and communication from health authorities describing the rationale for extended intervals and increased age of screening initiation with HPV-based screening, Canadian women may be reluctant to accept these changes. To confirm our findings, larger nationally representative samples would be needed. Our study results can inform future investigations of women's preferences for cervical cancer screening, as well as inform public health communications surrounding potential policy changes. As Canada transitions to HPV-based screening, it is essential that public health authorities adequately inform women about the rationale for, and advantages of extended screening intervals and increased age of screening initiation.

Data availability statement

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

Ethics statement

This study received ethical approval from the Research Ethics Board of The Integrated Health and Social Services University Network West-Central Montreal (CIUSSS-CO) (Project ID: 2021-2632). The patients/participants provided their written informed consent to participate in this study.

Author contributions

PZ and OT completed data analysis and wrote the first draft of the manuscript. BH, GG-M, LS, JB, GO, and ZR provided critical feedback on manuscript revisions. ZR supervised all stages of the project. All authors had substantial contribution in study conceptualization and design. All authors approved the final manuscript.

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Conflict of interest

JB's employer, the Australian Centre for the Prevention of Cervical Cancer, has received donated tests from HPV test manufacturers for research and validation studies.

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.962039/full#supplementary-material

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Evaluation of stroke health education for primary school students in Dali, China

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Objectives: To provide us with some evidence to develop more targeted stroke intervention strategies, improve the health awareness of stroke among children, and advocate the health promotion campaign of "small hands holding big hands" among parents and children, we have conducted a health education program on stroke among primary school students in Dali.

Methods: This study has applied stratified random cluster sampling in Dali of Yunnan, China. We compared the improvement of students' knowledge of stroke before and after our health education program in primary school students of Dali in October 2020. Data were collected through 3 rounds of survey by using the same questionnaire.

Results: There were 215 participants aged 7−8 years old sampled in the first phase of the study and 145 participants in the follow-up study. The knowledge of stroke among the participants was relatively low in the pre-intervention survey. After the health education, all the indicators on stroke knowledge were improved. The correct rates in stroke definition, sequelae, and "1-2-0" identification were increased from 0 to 66.05%, to 53.95% and 64.19%, respectively, in both pre-intervention and post-intervention surveys. The correct rate of stroke knowledge was about 4.83−92.41% 3 months after the intervention. The mean score of the questionnaire was 4.25 ± 0.19 in the pre-intervention survey, and that was 15.85 ± 0.27 in the post-intervention one. The mean score was 14.02 ± 0.28 post-3-month test. The score in the 3-month survey after the intervention was 11.55% lower than that in the post-intervention score.

Conclusions: The effect of stroke-related knowledge in the health education program for children is improved significantly and this can last for 3 months but it also had attenuation. We should repeat pertinent health education among students.

KEYWORDS

stroke, health education, effect, children, evaluation, ethnic

Introduction

According to the WHO, cardiovascular diseases (CVDs) are the leading cause of death globally, with an estimated 17.9 million lives taken each year. Also, the cause of over four out of five CVD deaths is attributed to heart attacks and strokes (1). Today, China bears a heavy burden of CVD (2). In 2018, the crude death rate of stroke was 149.49/100,000 among Chinese residents, accounting for 22.33% of the total number of deaths. Stroke was ranked as the third leading cause of death in China (3). A study has shown that the incidence of stroke was 6.2% among Bai Ethnic people aged over 35 years in Jianchuan County, Dali of Yunnan in 2018 (4), which was higher than that of adults in China. The rapid changes in lifestyle and dietary habits have made younger people more vulnerable to stroke in recent years (5). Children who had experienced early childhood stroke were at particular risk of alterations in cognitive functions (6). Moreover, epidemiological evidence of stroke burden among Dali residents was lacking. Only patient-specific studies have shown that the factors associated with stroke in Dali residents were age, blood glucose, blood lipids, daily barometric pressure, and daily air temperature (7, 8). Therefore, it is important to improve children's knowledge of stroke and its prevention.

Health education among primary school students has proved to be significantly effective in many studies (9–11). The students were in the critical age of forming the right health concepts with strong learning acceptance, moreover, their health literacy could affect that of the whole family (9, 12, 13). In the Netherlands, students can play a vital role when a stroke occurs by recognizing the signs of a stroke and calling 911 immediately (14). Less research was carried out and reported in China. The reported studies in foreign countries have mainly adopted FAST (Face, Arm, Speech, and Time) to capture a memory in stroke education (15). However, this did not work well due to the language barrier among Chinese adults (16). There have been no related studies on the methods of stroke health education and its effectiveness evaluation among ethnic children.

This study has selected the children as our study population and Dali prefecture as our survey location. It was the first intervention to improve children's stroke awareness in Yunnan. The study aimed to explore the methods of stroke health education for children and to improve children's awareness of stroke health. It is expected to provide us with some evidence for developing more targeted stroke intervention strategies in Yunnan.

Materials and methods

Study design

The study was a follow-up study with data that were generated from the Students' Surveys carried out in Dali of Yunnan from October 2020 to January 2021. The survey was conducted in Dali City of Yunnan province. According to the list of primary schools in Dali City, the survey school was randomly sampled by the end number of the random selecting banknotes. The survey grades and classes were also randomly sampled in the survey school by the end number of the random selecting banknotes. The study participants were recruited by cluster sampling from a sample primary school in Dali City, Yunnan, taking both representativeness and randomness into account. All the students in grades 1 and 2 were eligible to be recruited for our study. We provided stroke health education for the recruited students, and evaluated the educational effect before and after intervention in 2020 and that in 3 months after intervention in 2021. The surveyed students remained consistent from October 2020 to January 2021. Those who were not willing to sign the informed consent were excluded. All participants and/or their parents/guardians provided written informed consent before the survey. There were 215 participants aged 7–8 years old in the first phase of the study. Affected by the epidemic of COVID-19, the follow-up study used an online survey tool WJX.cn (http://www.wjx.cn) to collect data. The contents were kept the same in different surveys of this study. In the follow-up survey, only 145 students met the deadline for the online questionnaire.

Data collection

Data were collected through a questionnaire, which was designed by the research group and used in all the study surveys to measure the participants' understanding of stroke. The questionnaire mainly collects information about the participants' demographic features, their knowledge about stroke and its sources, such as its definition, attacking organ, risk factors, symptoms, identification (three-step method of identification of various problems), treatments, related sequelae, and meanings of about 120 "strokes". The full score of this questionnaire was 22, with 7 on risk factors of stroke, 5 on typical symptoms, 2 on treatment methods, 4 on sequelae, and 4 on "Stroke 120".

Before the intervention, students filled out the pre-intervention questionnaire, from which we generated our baseline data. Then, participants watched a cartoon educational video, "Stroke 1-2-0" (1-2-0 indicated a three-step identification method) (Figure 1). The message delivered in this video included the following: "1" face droop, "2" arm weakness, "0" speech affected/slurred," and "120" to call the ambulance. After watching the video, some participants shared their personal experiences about stroke, and what they would have done differently based on their new knowledge learned. After this, a professional investigator performed 1-2-0 again and introduced the meaning of stroke, its risk factors, symptoms, treatments, and related sequelae. The Q and A was finally added to enhance the students' understanding of stroke.

FIGURE 1
The educational videos for stroke 1-2-0.

Assessment of the improvement in students' knowledge was carried out twice by the same questionnaires. One was carried out immediately after the education (post-intervention), and the other was 3 months after intervention (follow-up). The three-month follow-up questionnaire was given without noticing and collected data online by a web application of "questionnaire star". The students had limited time of answering the questions. The students' completion times were studied qualitatively before and after the field intervention (pre-intervention and post-intervention).

Statistical analyses

The primary data analysis was conducted in 2021. All data were analyzed using SPSS 21.0 software. Differences in the mean score of survey questionnaires were compared using the ANOVA test. The correct answer rates for the questionnaire in different surveys (pre-intervention, post-intervention, and follow-up after 3 months) were calculated and stratified by gender, ethnicity, and grade subgroups. Univariate methods were not used to estimate P-value for differences by gender, ethnicity, and grade because high statistical power was achieved from the large sample sizes. Statistical significance was defined as $P < 0.05$.

Results

Population demography

A total of 215 children of 7- and 8-year-old primary school students were included and intervened, and they completed both pre-intervention and post-intervention questionnaires in October 2020. All of those who had received the intervention and completed survey questionnaires were included in the analysis, with 113 boys and 102 girls. The average age was 7.59 ± 0.49 years old. There were 84 students of Han people, 92 Bai ethnic people, and 39 people of other ethnicities. No significant difference was observed in the distribution of participants between boys and girls ($P > 0.05$), and only 145 of them completed the follow-up questionnaire in January 2021.

Baseline data in pre-intervention

As shown in Table 1, the Chi-square test found a significant difference in terms of treatments among the students whose mothers held different jobs ($x^2 = 6.15$, $P = 0.05$) in pre-intervention. There were no differences in other indicators. The students' knowledge of stroke was relatively poor in pre-intervention, especially in its definition, sequelae, and "1-2-0" identification. No one knew them.

Assessment of the stroke knowledge levels in pre-intervention, post-intervention, and follow-up in 3-month surveys

Students took an average of 20 min to finish the questions at the beginning of the survey. Then, the time of answering the same questions took an average of 10 min in the post-intervention survey. The time of answering the questionnaire in the post-intervention survey was way shorter than that in pre-intervention. The speed of the response to the stroke questions post-intervention was quicker than that of pre-intervention.

The Chi-square test found a significant difference in the students' levels of stroke-related knowledge in pre-intervention, post-intervention, and follow-up surveys ($P < 0.01$).

As shown in Figure 2, after the health education, all the indicators of stroke knowledge were improved. The correct rates of the questionnaires in two post-intervention surveys were higher than that in pre-intervention, especially in the immediate post-intervention survey. However, the correct rate in the follow-up survey was lower than that in the immediate post-intervention one. The correct rate of stroke knowledge was about 4.83–92.41% (the rate is of different questions) 3 months after the intervention. The indicators that achieved better intervention effect were stroke definition, stroke organ, and the meaning of 1-2-0.

Health education effect

As shown in Table 2, the ANOVA test found a significant difference in all indicators to measure stoke knowledge of in three surveys. The mean score of the overall questionnaire in pre-intervention was 4.25 ± 0.19., which increased to 15.85 ± 0.27 in the post-intervention. Then, it dropped to 14.02 ± 0.28 in the 3-month follow-up test. The mean score in the 3-month follow-up test was 11.55% lower than that in the post-intervention score. Despite that, the students' knowledge of stroke was improved after our intervention ($F = 681.21$, $P < 0.01$), especially in terms of stroke risk factors, symptoms, sequelae, and 1-2-0 identification. In the follow-up survey, the mean scores were also low in terms of stroke attacking organs, its treatments, and "1-2-0" identification (Table 2).

Source of health information

The top three sources of health knowledge were television (57.22%), doctors (55.83%), and teachers or school bulletin boards (55.56%).

TABLE 1 The correct rate of stroke knowledge of primary school students in pre-intervention in Dali, Yunnan, China.

Subsection	N	Stroke definition	Attacking organ	Risk factors	Symptoms	Treatments	Sequelae	1-2-0 identification
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gender								
Boys	113	0	39 (34.51)	2 (1.77)	1 (0.88)	2 (1.77)	0	0
Girls	102	0	34 (33.33)	2 (1.96)	1 (0.98)	3 (2.94)	0	1 (0.98)
Age								
7	88	0	25 (28.41)	0	1 (1.14)	3 (3.41)	0	0
8	127	0	48 (37.80)	2 (1.57)	3 (2.36)	2 (1.57)	0	1 (0.79)
Ethnic								
Han	84	0	27 (32.14)	2 (2.38)	2 (2.38)	2 (2.38)	0	0
Bai	92	0	31 (33.70)	2 (2.17)	0	1 (1.09)	0	1 (1.12)
Other	39	0	15 (38.46)	0	0	2 (5.13)	0	0
Area								
Country	89	0	31 (34.83)	2 (2.25)	1 (1.12)	3 (3.37)	0	1 (1.12)
City	126	0	42 (33.33)	2 (1.59)	1 (0.79)	2 (1.59)	0	0
Father's ethnics								
Han	119	0	40 (33.61)	3 (2.52)	2 (1.68)	3 (2.52)	0	1 (0.84)
Bai	70	0	23 (32.86)	1 (1.43)	0	1 (1.43)	0	0
Other	26	0	10 (38.46)	0	0	1 (3.85)	0	0
Mother's ethnics								
Han	111	0	35 (31.53)	3 (2.70)	2 (1.80)	2 (1.80)	0	0
Bai	78	0	28 (35.90)	1 (1.28)	0	1 (1.28)	0	1 (1.28)
Other	26	0	10 (38.46)	0	0	2 (7.69)	0	0
Father's education level								
Low	15	0	6 (40.00)	0	0	0	0	0
Middle	92	0	26 (28.26)	1 (1.09)	1	3 (3.26)	0	0
High	108	0	41 (37.96)	3 (2.78)	1	2 (1.85)	0	1 (0.93)
Mother's education level								
Low	15	0	3 (20.00)	0	0	0	0	0
Middle	105	0	33 (31.43)	1 (0.95)	1 (0.95)	4 (3.81)	0	0
High	95	0	37 (38.95)	3 (3.16)	1 (1.05)	1 (1.05)	0	1 (1.05)
Father's job								
Physical worker	192	0	62 (32.29)	3 (1.56)	2 (1.04)	5 (2.60)	0	0
Brain worker	23	0	11 (47.83)	1 (4.25)	0	0	0	1 (4.35)
Mother's job								
Physical worker	184	0	57 (30.98)	4 (2.17)	2 (1.09)	5 (2.71)*	0	1 (0.54)
Brain worker	31	0	16 (51.61)	0	0	0	0	0

N = 215, *P < 0.05.

Discussion

This study was the first to conduct a localized health educational intervention for primary children in Dali City of Yunnan, China. It has generated some useful information to inform health education on stroke for children and provide insights into preventing and controlling children's stroke in Yunnan ethnic prefectures.

It is evident from our study results that students' knowledge has been greatly improved in terms of stroke and its identification. For example, the correct rates of stroke definition, sequelae, and "1-2-0" identification were increased from 0 to 66.05%, to 53.95 and 64.19%, respectively, after the intervention. In addition, the correct rate of stroke definition kept increasing to 85.52% in 3 months after the intervention. However, the improvement was not observed 3 months after the intervention.
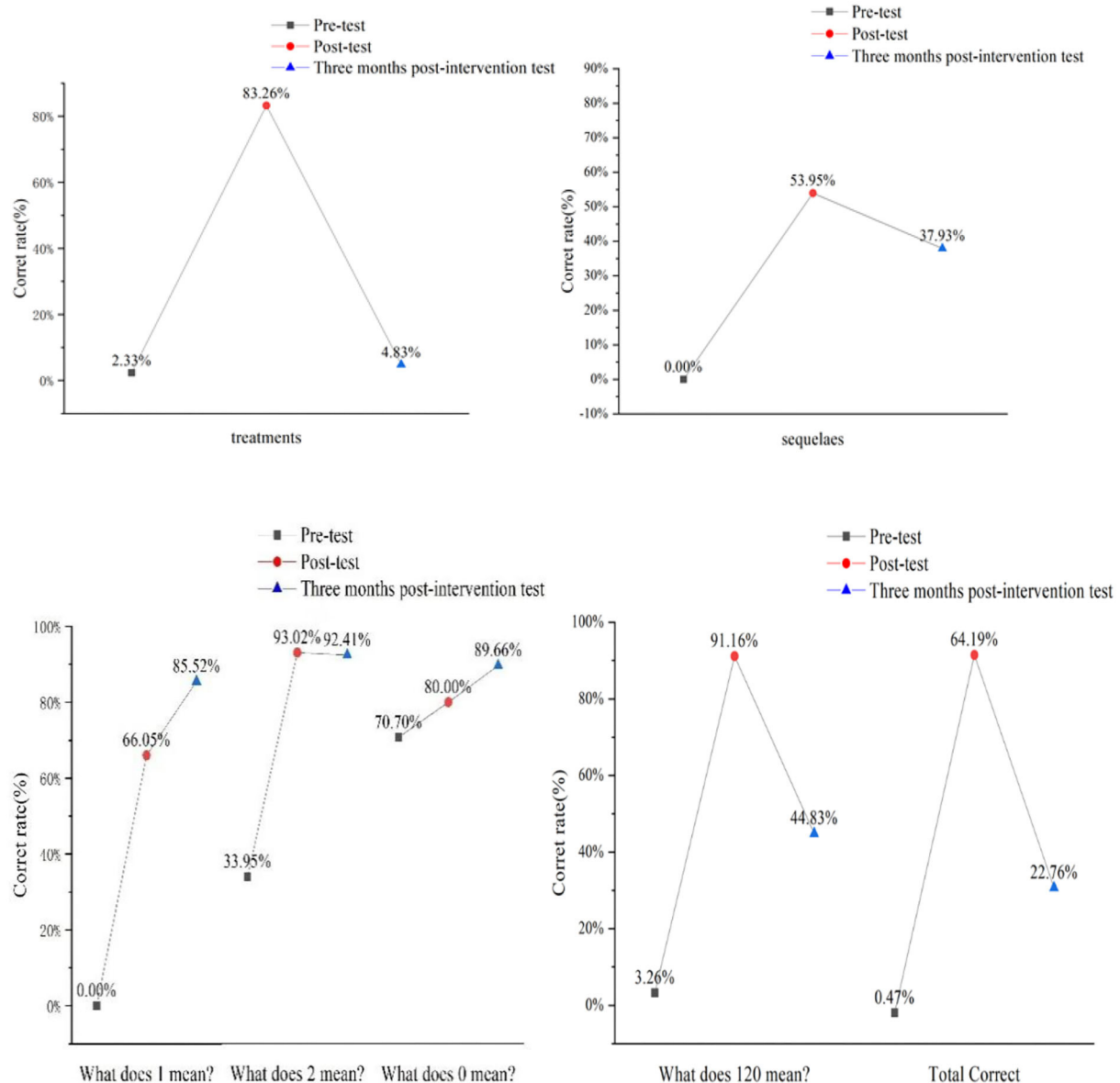
FIGURE 2
Assessment of the stroke knowledge in pre-intervention, post-intervention, and follow-up surveys.

The correct rates of sequelae and "1-2-0" identification were decreased to 37.93 and 22.76%, respectively, in 3 months after the intervention. The mean score in the follow-up survey was 11.55% lower than that in the post-intervention one. This decrease could be explained by Ebbinghaus' memory curve. This indicated that the health education program on stoke had attenuation despite the effects achieved among children. The correct rate of stroke knowledge was about 4.83–92.41% in 3 months after the intervention, which was lower than that in the study of Shigehatake (56%) (16) and Li X in Shanghai (84.4%)

(17). Therefore, we should repeat pertinent health education programs among students.

The materials used in this health education program was presented in cartoons and hip-hop song. The study found that the manner of delivering stroke health education to children was essential to ensure the effectiveness of health education. Age-targeted education can significantly raise the awareness of stroke in children. In the following study, we will pay attention to making the health education materials match the cognitive characteristics of children in the context of local culture (18, 19).

TABLE 2 The pre-intervention, post-intervention, and follow-up evaluation of stroke knowledge score of primary school students for stroke in Dali, Yunnan, China (means $\pm$ SD).

Subsection	Pre-intervention	Post-intervention	Follow-up	F	P
	($N = 215$)	($N = 215$)	($N = 145$)		
Stroke definition	0.00 ± 0.00	0.66 ± 0.03	0.86 ± 0.03	331.82	0.00
Attacking organ	0.34 ± 0.03	0.93 ± 0.02	0.92 ± 0.02	184.18	0.00
Risk factors	2.07 ± 0.12	5.37 ± 0.14	5.36 ± 0.14	211.71	0.00
Symptoms	1.17 ± 0.08	3.91 ± 0.09	3.25 ± 0.09	307.58	0.00
Treatments	0.27 ± 0.03	1.80 ± 0.03	0.57 ± 0.05	524.17	0.00
Sequelaes	0.40 ± 0.05	3.19 ± 0.08	3.07 ± 2.91	581.21	0.00
1-2-0 identification	0.05 ± 0.02	3.29 ± 0.08	1.59 ± 0.15	428.81	0.00

Meanwhile, we should also note that the top three sources of health knowledge were television (57.22%), doctors (55.83%), and teachers or school bulletin boards (55.56%). This indicated that the principal role of doctors, teachers, or school bulletin boards cannot be ignored in children's health education. School health education has traditionally been an effective public health strategy to help children develop a proper health concept. A study also confirmed that school health education had always been a good option for students to receive health education (20, 21). Because chronic diseases have a long progressing trajectory, children should be the priority group for future intervention in chronic disease prevention. We should carry out child-targeted health education on disease control and prevention in schools, and facilitate children to develop a healthy lifestyle, which would further eliminate their risk behaviors as early as possible and reduce the incidence of chronic diseases in young adults.

This study found that it was important to develop child-friendly health education materials in the future. Thus, how to develop a series of educational electronic animations and pamphlets for children will be the focus of future research.

Limitations

This study has a few limitations. Our study did not have a control group to measure the actual intervention effects, so the evaluation results had certain limitations. We will further expand the study population and scope in the future study and to provide generate robust evidence for the importance of stroke health education in children.

Conclusion

In conclusion, this study is the first one that utilized the successive follow-up data of 7–8 school-aged children of Bai ethnicity in Dali City of Yunnan, China. Especially, this study compared the effect of health education on stroke before and after intervention, even 3 months after intervention. The study revealed our intervention had significantly improved the knowledge of stroke among Bai ethnicity of 7–8 years old children of Yunnan, China.

In view that a number of benefits of conducting health education among children, such as effectively improving the health awareness of stroke, reducing high-risk behaviors, and enhancing the healthy lifestyle of the family, we should develop a health education model that could fit in with the psychology development of children and local culture to raise children's awareness on stroke prevention and control.

Data availability statement

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

Ethics statement

The survey was approved by the Medical Research Ethics Committee of Yunnan Preventive Medical Institute. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

YJY: conducted data collection, intervention, statistical analysis and manuscript design, writing, and editing. JD: conducted field survey, collected data, provided suggestions, and manuscript preparation. JQM: field survey, advised, conceived, and designed the work, and edited the final version of the manuscript. ZZS, SZ, and LTC: coordinated survey fields and advised. YL: analyzed data and drew figures. XW and HYQ:

conducted field survey, collected data, ill-disposed data, and analyzed data. JJC: provided suggestions, assisted in an English manuscript, and edited the manuscript. FL: analyzed data and provided suggestions. YPY: coordinated survey fields and conducted this study. YJY, JD, and JQM have full access to all the data in this study and takes primary responsibility for the final content. All authors have read and approved the final version of the manuscript.

Conflict of interest

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

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Public-private partnership (3Ps) in ensuring safe use of medicines: An Indian experience

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Adverse drug reactions (ADRs) are major concerns to the public health. To monitor ADRs and ensure patients' safety, the Pharmacovigilance Programme of India (PvPI) has been established by the Government of India in 2010. The programme is intact with the Public-Private Partnership (3Ps) in pharmacovigilance for quality services, better management of human resources and risk minimization. The present work is aimed at assessing the 3Ps engagement, performance and tangible outcomes in PvPI and also mapping of resources. The study was carried out for the period of 2011 to 2021 by assessing the various benchmarking tools such as 3Ps categorization, utilization of ADRs reporting tools, trainings, and the Individual Case Safety Reports' (ICSRs) quantity, quality and transmission for regulatory intervention (RI). Under PvPI, Central or State Government medical institutions/hospitals and public health programmes constitute public partners while private medical institutions/hospitals, pharmaceutical companies, corporate hospitals and professional bodies account for private partners. We observed that public partners extensively used ADR reporting form and toll-free helpline number while private partners used mobile based app and emails/post as preferred tools for reporting ADRs. Contribution of public sector in training programmes organized, stakeholders trained and sharing of resource materials was way higher than the private sector. The study revealed that 55.1 and 44.9% ICSRs were received from public and private partners, respectively during the study period. The quality completeness of data received from public partners was found to be 0.92/1 as compared to 0.46/1 from the private partners. The ICSRs data transmitted for RI process from the public and private partners (till 2018) was found to be 79 and 21%, respectively. In terms of sharing of resources for training and capacity building, the public sector played a major role. The 3Ps in India are enabled to establish a robust system for medicines' safety surveillance; however a more focused approach is required in mapping the resources.

Introduction

Adverse drug reactions (ADRs) are among dominant causes of mortality (1); and expected to pose a great threat to public health in near future (2). Therefore, prompt ADR monitoring and informing the authority for necessary intervention through a pharmacovigilance system is crucial for ensuring drug safety. According to the WHO, Pharmacovigilance (PV) is defined as the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (3). The ministry of Health & Family Welfare, Government of India launched its nationwide Pharmacovigilance Programme of India (PvPI) in 2010 and identified Indian Pharmacopeia Commission (IPC) as National Coordination Center (NCC) for the PvPI in 2011 with the aim of monitoring the safety of drugs consumed by the Indian population (4).

The usage of medicines in the private sector is consistently much higher than in the public sector. A Government survey in the year 2014 showed that more than 70% of illnesses were treated in the private sector, including clinics, hospitals and charitable institutions, a four percentage increase over a 10 year period (5). National Sample Survey Office (NSSO) reported that private doctors are the single source of treatment in both the urban and rural areas (5). Also, due to the exponential growth of private pharmaceuticals sector, there is an urgent need to provide handholding support to private sector to meet the challenges such as under reporting of ADRs, development of indigenous patient safety database and for mutual benefits including recognition and to avoid regulatory action (6). Engagement of healthcare professionals is key to success for Pharmacovigilance (7); Therefore, the alliance by the PvPI with public and private hospitals/academic medical institutions has resulted in establishing a robust system and tools for ADRs monitoring, reporting and assessment. In order to ensure seamless ADR-reporting, mobile app and helpline facilities have also been developed besides customized paper-based reporting form (8, 9).

The available scientific articles revealed that public-private partnerships (3Ps) is one of the key components in promotion of healthcare and can also influence intellectuals and policy decisions (10, 11). The 3Ps is also considered to be an important mechanism for ensuring sustainable development goals (12). As PvPI is being successfully implemented with the 3Ps using existing government systems and regulatory framework, wherever possible and aligned with the policies and strategies, the aim of this study is to assess the engagement, performance and tangible outcomes of the ongoing 3Ps activities in ensuring safe use of medicines in India. This will also identify barriers for equitable alignment in technical, policy and mapping of resources.

Study design

The study was conducted retrospectively for a period of ten years (2011–2021). The public and private partners, those formally recognized as ADR monitoring centers and informally engaged with PvPI for ADR-reporting and capacity-building were categorized accordingly. The training conducted and its outcome, resource-sharing and capacity-building were assessed. The Individual Case Safety Reports (ICSRs) provided by public-private partners were segregated from VigiFlow/VigiBase (a web-based tool owned by WHO-Uppsala Monitoring Center, Sweden and subjected to quantitative and quality completeness assessment. The quality completeness of the ICSRs was assessed as per the method established by Kalaiselvan et al., 2015 (13). The ICSRs of both public and private partners transmitted for regulatory intervention (RI) process were also assessed.

"3Ps"-categorization and engagements

Since its inception, the PvPI has been consistently engaged in identifying the partnering institutions both from public and private sector. The working relationship was gauzed through either formal Memorandum of Understating (MoU) or mutual understanding to attain common benefits. The present PvPI structure has a mixed set-up: where both the public (Government of India and Government of States and Union Territories) and private academic medical institutions/hospitals as ADR Monitoring Centers (AMCs) pan-India coexist. The 446 AMCs established during the study period were unique in nature and equally distributed in public and private sector; 224 and 222 AMCs in the public and private sector, respectively. The AMCs are primarily responsible for monitoring and reporting ADRs to PvPI. In addition, the PvPI has established a working relationship with other private entities such as Marketing Authorization Holders (MAHs) of pharmaceutical industries, corporate hospitals and professional bodies to attain the common goal of promoting the safety of medicines.

ADR reporting by "3Ps"-voluntary or mandatory

The private sector i.e., MAHs are mandatorily required to submit the adverse events associated with use of new drugs mandatorily (up to four years from the date of approval) to the National Regulatory Authority i.e., Central Drugs Standard Control Organization (CDSCO). In addition, the CDSCO also encourages MAHs to submit voluntary reports of ICSRs associated with medicines to PvPI. For the

FIGURE 1
Utilization of adverse drug reactions reporting tools to ensure safe use of medicines by public and private stakeholders under 3Ps.
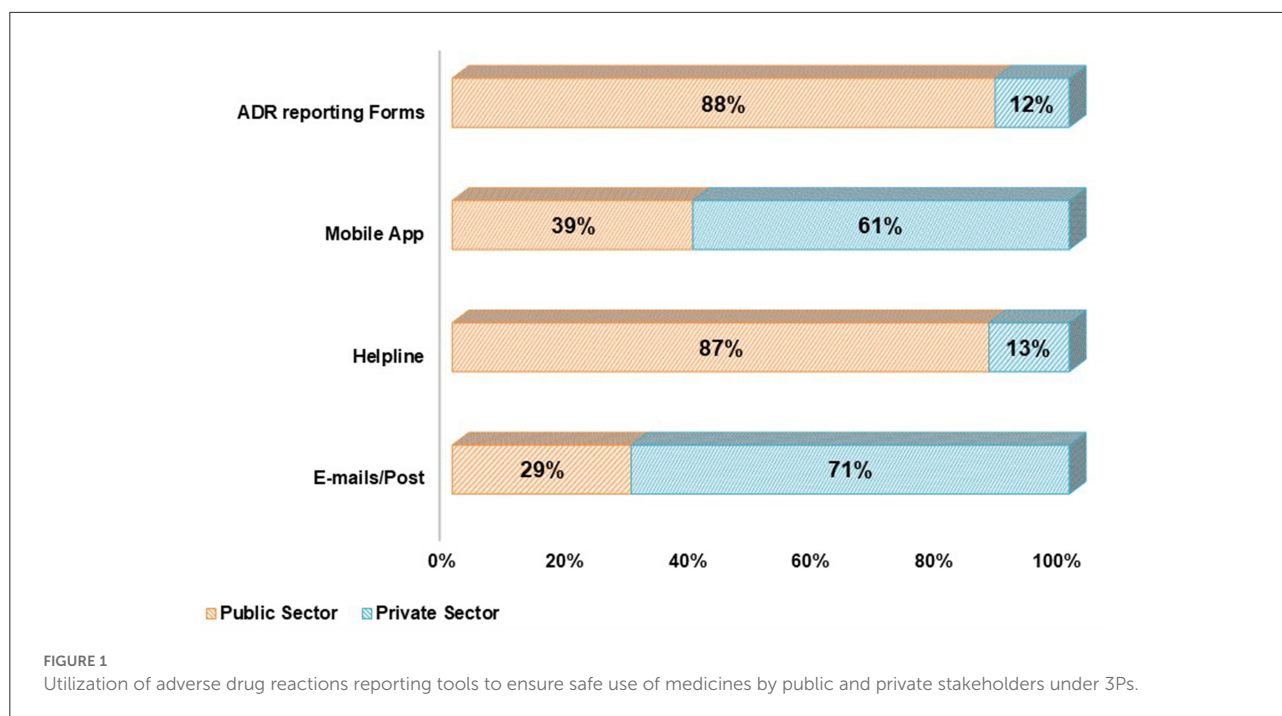
last ten years (2011–2021), 130 MAHs of pharmaceutical products have participated in the PvPI by reporting ADRs. However, ADR reporting by recognized AMCs under PvPI is primarily voluntary in nature. The PvPI encourages them as well as other healthcare professionals associated with corporate hospitals/clinics/professional bodies and government hospitals to report ADRs by solicited spontaneous (voluntary) method.

ADR reporting tools for 3Ps

Public and private partners were provided with multiple tools to report ADRs; the customized reporting form which is paper-based was often recognized as one of the most widely used tools for reporting ADRs but as per the feedback received from the stakeholders, it is a time-consuming tool. In order to overcome the shortcoming and enhance the stakeholders involvement to gain momentum, tools such as Helpline (toll free number 1800 180 3024) and mobile app were developed. Since 2014, PvPI has been accepting the electronic submission of both expedited and non-expedited ICSRs from MAHs in the Extensible Markup Language (XML) as per E2B guidelines (14). This tool was developed by MAHs at their own expenditure. We observed that ADR reporting tools such as paper-based reporting form (also available in various regional languages) and toll-free helpline number were mostly used by the public sector (88 and 87%, respectively). Private sector used mobile-based application and emails/post

by 61 and 71% respectively, while reporting ADRs to PvPI (Figure 1).

Training and capacity building

PvPI appoints a dedicated, qualified and trained human resource team at recognized AMCs (both public and private sector) to foster pharmacovigilance practices. Also, an AMC focal person (A focal person may have a degree in medicine, dentistry, pharmacy, clinical pharmacology, pharmacy practice or clinical research and possesses minimum 1 year experience in drug safety or pharmacovigilance) along with their team were continuously trained and provided with technical guidelines, ADRs reporting tools and other accessories by the PvPI for seamless functioning. All recognized AMCs were enabled to submit the ICSRs through VigiFlow. Besides, PvPI in alliance with MAHs of pharmaceutical products and professionals bodies such as Indian Medical Association, Indian Pharmacological Society and others exhorted them to receive ADRs from their quarters. Under 3Ps, private partners were urged to join for a professional cause to promote drug safety with no commercial interest.

PvPI conducted numerous training programmes during the period of 2011 and 2021 with the support of both public and private sector. The objectives of such training programmes were aimed at providing the basic concepts and understanding of ADR-reporting, tools and methods, causality

TABLE 1 Contribution of public–private partners in knowledge and resource sharing.

S. No.	Indicators	Contribution by public sector	Contribution by private sector
1.	Training programmes organized	2,468	1,508
2.	Healthcare professionals trained	126,602	65,233
3.	Impact of training programmes (Average % increase in ADR reporting after every subsequent training)	59%	41%
4.	Sharing of information/resource materials	75%	25%

assessment, regulatory pharmacovigilance and signal detection. The trained participants of public and private sector were geared to propagate the concept and adopt the practice of pharmacovigilance for mutual benefits. The trainings were organized by PvPI alone (managed with its own resources) where healthcare professionals of public and private sector participated or jointly organized by PvPI and private sector where the resources were mapped. During the period 2011–2021, in total, 3,976 trainings (2,468 by public sector and 1,508 by private sector) were conducted under the umbrella of PvPI to clear the concept and provide hands-on training on ADR-monitoring and reporting and translational/regulatory pharmacovigilance. Technical expertise available in both public and private sector was fully utilized in the training programmes. As many as 191,835 healthcare professionals, including doctors, pharmacists, nurses, drug regulators, patients' support-group and others, were trained during the study period. These training programmes were instrumental in enhancing reporting of ADRs. A significant average increase of 59 and 41% in ADR reporting was observed by public and private sector, respectively following training programmes. A contribution of 75 and 25% in publication of scientific articles, reviews and case studies were noted by public and private sector, respectively (Table 1). The major outcomes of these training programmes are development of a sense of responsibility and to raise awareness on what, how and where to report ADRs, and to ensure that mere reporting an ADR does not attract any legal implication for reporter. Taken together, these changes fostered the culture and quality of ADR-reporting in a big way.

3Ps' data generation-quantity, quality and signal detection

For the last ten years 584,015 ICSRs were generated using the 3Ps' approach and assessed by the PvPI, of which 321, 657 (55.1%) were reported by the public AMCs and its periphery public sector (Central, States/UTs) academic institutions/hospitals, public health programmes such as National Tuberculosis Elimination Programme, National AIDS

control programme, National Center for Vector Borne Diseases Control (NCVBDC) and Universal Immunization Programme. A total of 262,358 (44.9 %) ICSRs were identified as reported by private sector which includes the AMCs under private ownership and MAHs of pharmaceutical products. Around 71 and 29% of the ICSRs reported by the public and private sector, respectively, accounted for the use of generic medicines and nearly 55 and 45 % of the ICSRs reported by the public sector and private sector, respectively, accounted for branded medicines (till 2018). The quality of ICSRs submitted using 3Ps' approach was assessed during the study period (2011–2021). As per the UMC guidelines, the quality completeness score for ICSRs ranges from 0.07 to 1 (15). The average quality of ICSR data provided by public partners was found to be 0.92 as against 0.46 by the private partners. The quality of data plays an important role in clinical assessment and thus identifying new safety signals. The new signals or meaningful findings thus generated were communicated to CDSCO for making an appropriate regulatory decision. Most of the ICSRs received from the private sector, unlike ICSRs received from the public sector, were lacking in information such as the identifiable reporter, reaction details, laboratory investigation details and causality assessment. The ICSRs contributing to detecting safety signals (a new or unknown ADR, not reported previously) and other RIs from public and private sector have been illustrated in Figure 2.

3Ps impact in international arena

The collective approach by 3Ps witnessed a successful National Regulatory Authority (NRA) assessment for vaccines where PvPI played a key role in enhancing the reporting of adverse events associated with vaccines. The 3Ps' contribution helped Indian NRA to get the highest benchmarking score for the tool of Vigilance for the assessment year 2017. As per data available at WHO-Uppsala Monitoring Center, India is one of the top 10 ADR-reporting countries in terms of quantity and highest among all in terms of quality (16, 17). Also, India-specific data contributed to WHO-UMC in detecting the

FIGURE 2
Contribution of public and private stakeholders in individual case safety reports generation, management, quality of reports and regulatory interventions.
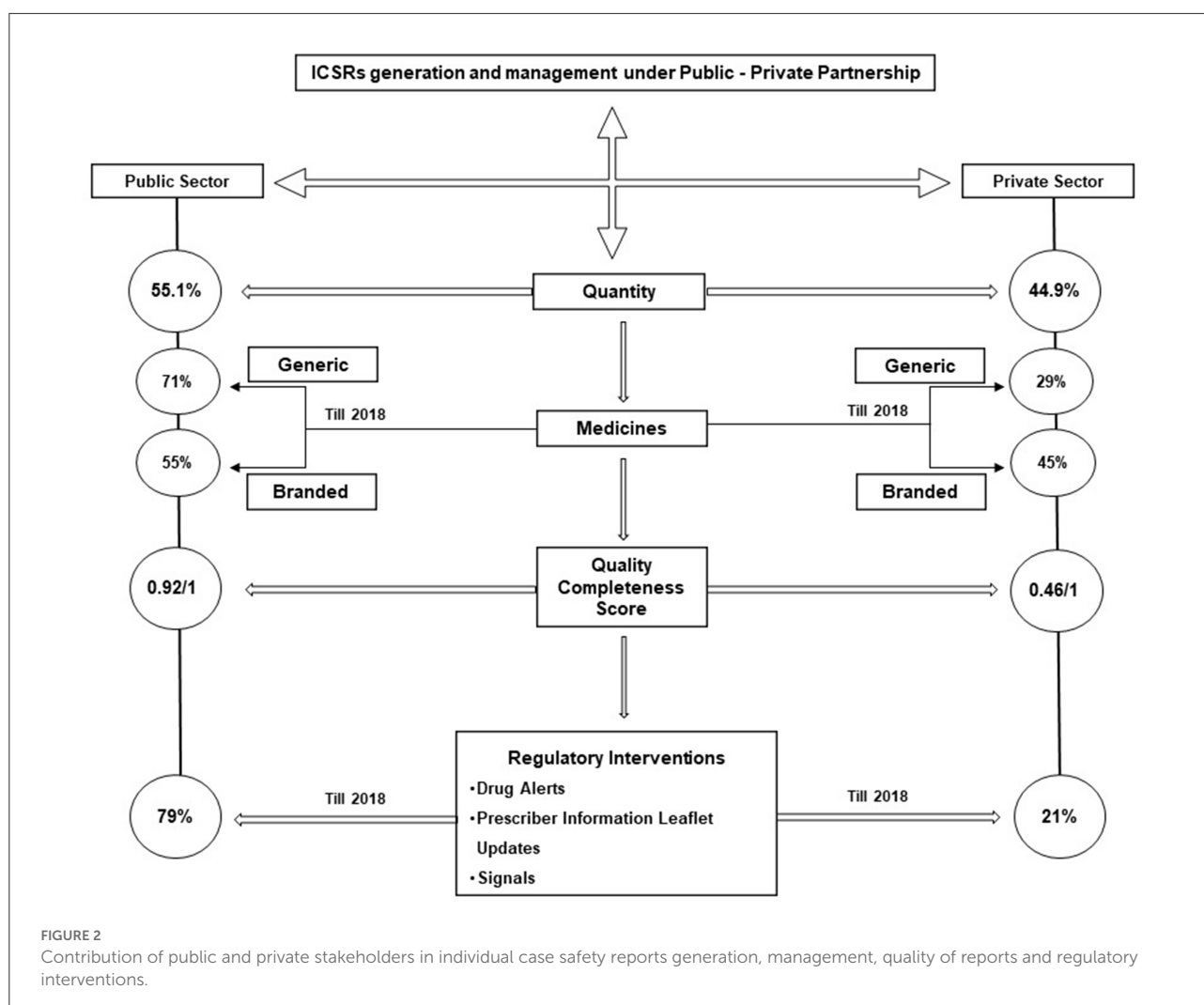
global signals associated with use of drugs and vaccines. The India-specific drug-safety information is regularly published in WHO pharmaceuticals newsletter. By collective efforts and its 3Ps deliverables, the PvPI has been recognized globally by the WHO as one of its Collaborating Centers (WHO-CC) for pharmacovigilance in Public Health Programmes and Regulatory Services in 2017 for 4 years and recognition is further extended to four years i.e. upto 2025.

Discussion

Though PvPI has played a key role in establishing AMCs in the private sector, the quantity and quality of ICSRs reported by the public sector hospitals during the period 2011–2021 has been appreciably high (18). Aimed at fostering the culture of reporting by 3Ps, the PvPI has contributed by sending circulars, appreciation letters, feedback, etc. As per the feedback received,

the reasons for low reporting vary between the public and private sector. More workload or lack of time is the major concern for public sector whereas in the private sector the perception is that reporting of more ADRs may affect the reputation of the hospitals/organization concerned. The PvPI, therefore, addresses the issues by education and advocacy to the hospital management and team of healthcare professionals that ADR-reporting is voluntary in nature entailing no punitive action. Even the quality completeness score of reports received from the public sector is higher than those received from the private sector. The quality score of the reports received from private sector is low as they do not want to reveal complete information of the ADRs, fearing litigation. The number of ICSRs contributing to identifying new signals or update of the package insert has been mostly from the public sector. The public sector contributed significantly higher reporting of ADRs associated with the use of generic as well as branded medicines as compared to the private sector.

The PvPI has played a pivotal role in capacity-building at both public and private sector, enabling the organizations to strengthen their competency in developing and implementing Good Pharmacovigilance Practices (GVPs). The public sector shared/spent around 75% volume of the resource/finance as against the remaining 25% by the private sector. The tailor-made pharmacovigilance training course developed by the PvPI has been effectively utilized to familiarize professionals with the concept of ADR-reporting and management. In terms of participation and organizing the training programmes, both private and public sector have played an equal role. It has been observed that the reporting of ADRs after each level of training has increased exponentially.

The PvPI has successfully attempted to excel the practice of pharmacovigilance with the introduction and promotion of emerging technologies in consonance with International standards. At present, the PvPI operates with full financial support by Ministry of Health & Family Welfare, Government of India. The private sector will require arranging resources for providing training to the stakeholders as the current drug regulation in India makes pharmacovigilance mandatory for MAHs. This will also require private partners to take ownership of the activity. The 3Ps in India have paved the way for generation of nearly 0.58 million ADRs in PvPI database and helped the Indian regulatory authority to be self-reliant in RI process. However, to achieve the sustainable development goal of PvPI, there is an urgent need for developing/leveraging ADR reporting/analyzing technologies such as mobile app, e-reporting and making these enabling tools available to 3Ps in a more effective way which will also help reduce the overall cost of PV system operation (19, 20). Harmonized and partnered approach is essential, too, to save the cost and mapping of resources. The PvPI or public funding alone may not be sufficient to meet the challenges of pharmacovigilance. However, the private sector participation and sharing of the resources for pharmacovigilance needs to be enhanced in future. Though, 3Ps in particular to healthcare settings offer many inherent advantages such as access to quality private services, trained manpower, efficient management of human resources, minimization of risk to both, public and private partner, better community relationships, business development or investment opportunities for private sector, sustainability for integrating

private partner in public health system remain a major challenge (21).

Conclusion

The 3Ps in India are aimed at establishing and implementing a robust PV system to monitor the safety of medicines. This approach is proven and tested and will sustain the harmonized and partnered strategy among all 3Ps stakeholders besides being cost-effective. It is expected that private sector will contribute more in near future for ensuring safe use of medicines in India.

Data availability statement

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

Author contributions

Conceptualizations, methodology, and data analysis by VK and SS. Writing—original draft preparation by VK, TS, and SS. Writing—review and editing by SS and SA. Project administration by VK and RR. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Audit and feedback in cardio– and cerebrovascular setting: Toward a path of high reliability in Italian healthcare

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Adopting audit and feedback (A&F) strategies could be a suitable healthcare intervention to fulfill the challenge of monitoring and improving clinical guidelines in evidence-based medicine. Indeed, A&F is used to encourage professionals to better adhere to standard guidelines to improve healthcare performance. Briefly, an audit is an inspection of professional practice in comparison to professional standards or targets whose results are subsequently communicated to professionals in a structured manner. Although A&F strategies have been adopted in several time-dependent settings, such as for acute myocardial infarction (AMI) and stroke, interest of audits in rehabilitation care is also emerging. Recently, the Italian Ministry of Health has funded a national network project called EASY-NET, whose main objective is to evaluate the effectiveness of A&F strategies to improve healthcare practice and equity in various clinical and organizational settings in seven Italian regions. Last but not the least of these regions is the Sicily, represented within the project by the IRCCS Centro Neurolesi Bonino-Pulejo of Messina as the work package 7 (WP7). The EASY-NET WP7 is focused on the effectiveness of A&F strategies in both AMI and ischemic stroke setting, from acute to rehabilitation process of care. In this study, we described the study protocol, including the study design and methodology, providing a detailed description of the new model of A&F based on telemedicine, and discussing the possible challenges of this project.

KEYWORDS

audit and feedback, care pathway, ischemic stroke, acute myocardial infarction, neurorehabilitation

Introduction

Diseases of the circulatory system are the leading cause of death in Europe (∼37.1% of all deaths) (1), and the most common include ischemic heart diseases (heart attacks) and cerebrovascular diseases (strokes). Notably, ischemic stroke is also the first cause of permanent disability and the second cause of dementia, with incidence oscillating between 7 and 23% in the first year after the event (2).

In Italy, >100,000 hospitalizations for acute myocardial infarction (AMI), as well as for stroke (∼80% are ischemic strokes), occur every year, with 1-year mortality rates in the range of 10 and 30% (3, 4), respectively. Although the most recent statistics showed a decline in mortality, as well as a reduction in disability, premature death, and early incidence, the burden of cardio- and cerebrovascular diseases is still high, and it is expected that, within the next 20 years, there will be an increase of >30% of the prevalence rates because of the aging population (2, 5).

Implementing clinical guidelines into practice is one of the most significant challenges of evidence-based medicine. Indeed, there exists a large gap between ideal and actual care provided to such patients on which the translational research is focusing (6, 7). Previous studies showed a good level of effectiveness reached through tailored interventions for quality improvement, which are often complex and heterogeneous ranging from passive intervention as the dissemination of printed educational materials (e.g., guidelines, journal articles) (8) to active interventions as outreach visits or group education (e.g., lectures, workshops or facilitated interactive group discussions) (9), and audit and feedback (A&F) strategies (10).

A&F strategies are a well-known healthcare intervention, defined by Brehaut and Eva as "a summary of clinical performance over a specific period of time (audit), and the provision of that summary (feedback) to individual practitioners, teams, or healthcare organizations" (11). The main purpose is the improvement of quality, safety, and efficiency of the care, based on a systematic review of professional performance and the monitoring of key indicators of process quality. Essentially, an *ad hoc* team examines and verifies whether a specific clinical practice has been performed in adherence to guidelines and hospital protocols (audit), backing professionals with a report showing how they perform in relation to their peers, standards, or targets. In addition, they can identify possible actions in order to change current practice and improve performance (feedback). Audits can be used to assess individual healthcare workers' performance or that of teams, departments, hospitals, or regions.

The reliability of A&F is conditioned on the availability of collected data, method of analysis, and time devoted to this activity. Indeed, the whole process would require a well-established system of event report, data collection, purposeful management of

Abbreviations: AMI, Acute myocardial infarction; A&F, audit and feedback; WP7, work package 7; QIs, quality indicators; COPE, Coping Orientations to Problem Experiences; RHS, Regional Health System; ICD-9-CM, International Classification of Deceases, 9th revision, Clinical Modification; EQIs, emergency quality indicators; RQIs, rehabilitation quality indicators.

the available information, appropriate communication of the results, careful identification of the recipients, and a time schedule for monitoring and control. Moreover, cost-effectiveness likely depends on the clinical topic (12).

Over the last two decades, A&F strategies have been used for any area of healthcare, i.e., preventive, acute, chronic, and palliative care. With the aim of improving the quality of performance, reducing failure rates, and increasing safety, as well as care access, A&F strategies have been adopted also in time-dependent settings such AMI and stroke (13–16). Any step contributes to accomplish the "mindfulness" of a successful organization, acting in the manner for individuals and teams to interact and share information, and the capability to act following that understanding.

Although most studies have focused on practice areas of the emergency and acute setting, there has recently been a growing interest in audits of rehabilitation care (17). However, it remains unclear whether A&F is more effective than other quality improvement interventions, especially when combined with any of these interventions (12). Therefore, the implementation and testing of new models of A&F in the cardio- and cerebrovascular area to improve the quality of the clinical practice from acute to rehabilitation hospitalization are needed.

The Italian research project EASY-NET

On 15 April 2019, the Italian network project EASY-NET was started (18), which was funded by the Italian Ministry of Health and whose main objective is to evaluate the effectiveness of A&F strategies in order to improve healthcare practice and equity in various clinical and organizational settings in seven Italian regions. Therefore, EASY-NET focuses on the processes of care and/or patient outcomes that are strongly correlated with processes of care, effectiveness, and safety, besides other aspects of performance, such as timeliness, efficiency, and equity. Within the general project, the IRCCS Centro Neurolesi Bonino-Pulejo of Messina is responsible for work package 7 (WP7), focused on the effectiveness of A&F strategies in both AMI and ischemic stroke settings, from acute to rehabilitation process of care.

This article describes the EASY-NET WP7 study protocol, reporting the study design and methodology, and discussing expected results and challenges of this project. In addition, a detailed description of the new model of A&F based on telemedicine protocols and the intervention of an experienced psychologist is provided. The step-by-step project is reported in the flowchart depicted in Figure 1.

FIGURE 1
Step-by-step project procedures.
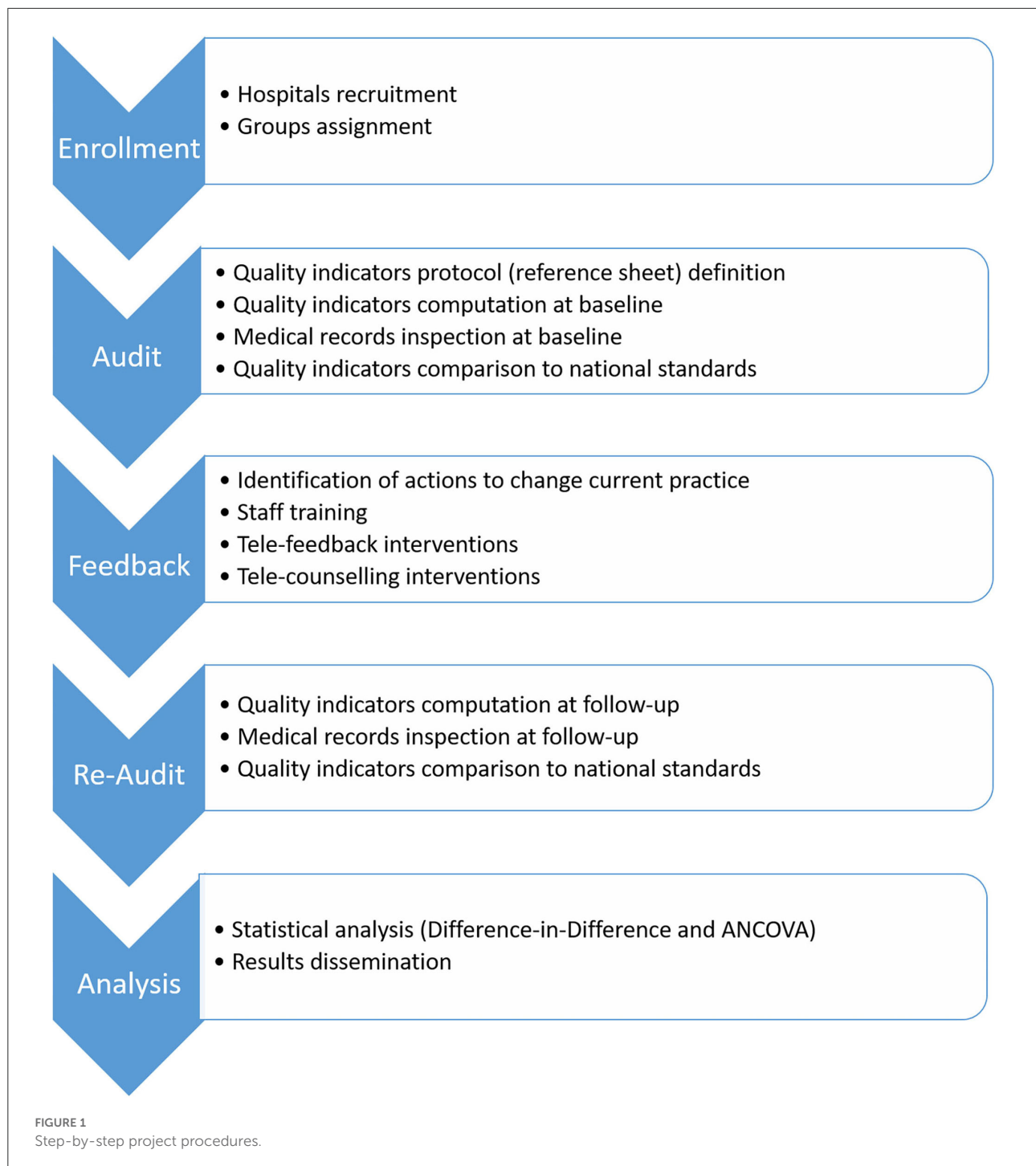
Methods and analysis

Study design

A prospective and quasi-experimental study design, since hospitals are assigned to the intervention or control group based on some characteristics, will be used to test the effectiveness of a new 1-year A&F program.

Setting and participants

Consent was requested from the healthcare managers of the eligible Sicilian hospitals (in the areas of Messina, Catania, and Palermo) to participate in this study. The target population of the A&F intervention are healthcare workers in the context of cardio- and cerebrovascular emergency (AMI and ischemic stroke) and in neurological rehabilitation (ischemic stroke).

Eligible hospitals for the acute setting include (i) an emergency room (ii) at least a service for the treatment of cardiovascular diseases (coronary units and/or interventional cardiology services); and (iii) at least a service for the treatment of cerebrovascular diseases (stroke unit and/or interventional neuroradiology services). Eligible hospitals for the neurorehabilitative setting are provided a neurological rehabilitation unit for stroke survivors.

Enrolled hospitals have been subdivided into two groups according to geographic area and some structural characteristics such as the hospital catchment areas for AMI and stroke. The first group (group 1 or G1) includes hospitals in which the traditional A&F procedure will be performed; the second group (group 2 or G2) includes hospitals in which the new A&F model will be performed. Table 1 shows the traditional A&F procedures and the new A&F model and their differences.

The A&F procedure: Traditional vs. new

For each setting (emergency and rehabilitation) and disease (AMI and stroke), a multidisciplinary team, including experts in the process of care in examination (e.g., risk manager, cardiologist, neurologist, physiatrist, and nursing coordinator), was constituted to conduct the A&F procedure, and a set of quality indicators (QIs) assessing hospital performance was selected and described in a specific reference sheet. Therefore, according to a checklist of information mandatory to QI computation, data were extracted and QIs computed.

Any highlighted gaps between the defined protocols and the observed management, as well as between the hospital QIs and national standards, represent the background for the planning of the hypotheses of corrective and educational interventions for healthcare professionals. On this basis, the A&F team identifies actions to change the current practice, according to the characteristics of each process of care in examination, following the corresponding guidelines and recommendations. Notably, the team sends its feedback to hospitals in the control group by email, thereby providing feedback interventions by using telemedicine to hospitals belonging to the experimental group.

The new A&F model includes a psychologist skilled in communication, who trains the A&F team to adopt an effective communication toward the recipients, reinforcing their relational techniques in the feedback phase. Thus, before the feedback, the team members undergo individual and group psychological screening through the administration of self-report tests in order to identify relational criticisms and plan effective therapeutic interventions. In addition, the psychologist, upon request, also conducts systemic therapeutic interventions aimed to correct those healthcare professionals' communication models that make the care process of the patients dysfunctional, through the use of remote information and communication technologies typical of the telemedicine.

Each center will be provided with a telemedicine platform useful for dual purposes: (i) to perform feedback as tele-counseling meetings, in which the responsible staff of the department subjected to the A&F intervention (primary and nursing coordinators) will take part, together with the A&F team and the psychologist, who will intervene on the relational processes when necessary and (ii) to perform therapeutic interventions on healthcare professionals belonging to the hospitals subjected to A&F.

Training and therapeutic intervention for effective communication

By administrating questionnaires and psychological tests, the psychologist identifies the communication criticalities of subjects providing the feedback and supports the team in effectively proposing the best-change strategies to healthcare professionals through the application of structured techniques ranging from the use of discussion and comparison techniques, which facilitate the processes of cognitive exchange and execution of tasks, up to problem-solving, simulation, and role-play techniques.

Therefore, after a careful examination of the problems reported by the team, the error and risk indicators will be considered through questionnaires and discussion groups. The psychologist will intervene on the relational. Timing and frequency of the meetings will be properly established, and they will involve the application of structure processes that could have led to the error. The sessions with the psychologist will include both individual and group interviews (19).

The structured techniques intervene in the group, giving it a temporary structure. The group is altered for the time provided by the technique, then returns to the original configuration, drawing the benefits gained. Among several structured techniques, the important ones are (19–23) as follows:

- Discussion and comparison techniques, which facilitate the processes of cognitive exchange, expression of the differences, creation of common codes, and performance of table tasks. Such techniques are based on the assignment of new stimuli, which can be individual, pairs, or subgroups (i.e., group divided into parts or subsets).
- Gathering techniques: "Ignite" the group meeting through self-presentation, tales of one's past, socialization, and knowledge.
- Ideation techniques: They are used to promote the creativity and invention, are carried out through brainstorming (initial phase of relaxation, chaotic phase of production of ideas, final phase of selection on the basis of rational criteria and shared), mind map (writing on the board of the free associations of the group around a concept, a network of concepts associated with each other is created), and guided imaginations (the operator speaks

TABLE 1 Traditional A&F procedures and the new A&F model and their differences.

	Traditional A&F	New A&F model	Differences
Audit preparation	- Establishment of a working group carrying out the audit. - Definition of reporting criteria.	- Establishment of a working group carrying out the audit. This includes the intervention of an experienced psychologist who carries out a screening on the working team dynamics in order to identify any criticalities in the relational approach. - Definition reporting criteria. The psychologist instructs the working group to adopt an effective mode of communication toward the audit recipients.	Compared with the traditional model, the new model includes the intervention of an experienced psychologist both at the stage of establishing the working group and at the stage of reporting criteria.
Clinical audit	- Definition of objectives. - Evaluation of "existing documents" by construction of appropriate checklist based on indicators produced. - Defining the strategy for data collection and analysis: methods, actions, recommendations, responsibilities, discussion, timing. - Conduct of Document Audit through document analysis: patient records, laboratories, radiology, pharmacy. - Processing data collected during audit and producing reports containing strengths and weaknesses of the process. - Sharing and communication of results (feedback phase): reports are traditionally sent *via* email.	- Definition of objectives. - Evaluation of "existing documents" by construction of appropriate checklist based on indicators produced. - Defining the strategy for data collection and analysis: methods, actions, recommendations, responsibilities, discussion, timing. - Conduct of Document Audit through analysis of documents: patient records, laboratories, radiology, pharmacy. - Processing of data collected during audit and production of reports. - Sharing and communicating the results (feedback phase): the audit team presents the results to the staff of the department undergoing the intervention, so as to discuss together the strengths and weaknesses of the process through tele-counseling sections operated with telemedicine devices positioned within the hospitals. The psychologist intervenes on the relational processes that could have induced the error (measured through error and risk indicators calculated by means questionnaires and focus groups).	Compared with the traditional model, the new model includes the intervention of an expert psychologist in the feedback phase, carried out with the support of telemedicine systems.
Implementation of improvement actions	- Definition of action plan. - Guidance and support for the change.	- Definition of action plan. During this phase, the psychologist supports the team in planning hypotheses for corrective action to be submitted to the healthcare workers, aimed at improving the organizational strategy. - Guidance and support for the change. Through the use of remote information and communication technologies typical of telemedicine, the psychologist intervenes on the communication patterns that have been able to make the care process of patients dysfunctional and implements techniques to reinforce the self-awareness and to activate the team by engaging them in precise activities.	Compared with the traditional model, the new model includes the intervention of an experienced psychologist in the phase of defining the action plan and in the phase of guiding and supporting for the change. In this latter phase the psychologist uses the telemedicine supports.
Monitoring of results	- Re-audit	- Re-audit	

to the group that is in a relaxed position inducing a series of evocative images).

- Production techniques: They are used to stimulate the action and characteristics of groups with instrumental targets.
- Problem-solving techniques: They are presented a problem to be solved through the analysis of critical cases likely to be read and discussed in order to make a decision.
- Simulation techniques: You simulate "step into the shoes of," through role-playing (role-playing, each member of the group plays a role and the focus is placed on the actor).
- Self-centered techniques: The focus of the group (point of greatest concentration of the group and the operator) is concentrated only on himself in the present moment. These techniques have an essential role in the growth of the group, which cannot be such if it lacks self-awareness.
- Directional techniques: They tend to send the group in a certain direction, minimizing the degree of freedom of the group itself. It is the operator who makes the decisions.
- Active techniques: These aim to "make people do," to activate the group by engaging it in specific activities. These techniques are very common in educational work.
- Reflective techniques: Self-centered techniques whose main purpose is to stimulate the group to look at itself. They structure the space–time coordinates, leaving everything else free: they make the defenses of evasion or denial of reality evident.
- Diagnostic techniques: They aim to take stock, offering concrete data of the situation.
- Cognitive, emotional, instrumental techniques: The balance of the group can be tilted starting from the cognitive, emotional, or instrumental fabric (knowing, knowing how to be, and knowing how to do).

Psychological assessment

The protocol began with an *ad hoc* questionnaire aimed at collect information on the sociodemographic data of healthcare workers and daily life habits in relation to their employment with particular reference to their work setting. Subsequently, a battery of self-reported questionnaires was administered.

The Coping Orientations to Problem Experiences (COPE) is a 60-item self-report questionnaire that evaluates the frequency of use of 15 different coping strategies (represented by four items each) that can be adopted to manage stressful situations. In addition, they can be summarized into five factors, namely, "social support" (score 12–48), "avoidance" (score 20–80), "positive attitude" (score 12–48), "problem oriented" (score 12–48), and "religion" (score 4–16). Due to differences in the number of items that represent the five factors, mean factor scores were computed based on the number of items. Higher scores indicate that a particular coping strategy is more frequently used (24).

Data source

Data concerning the two acute settings will be retrospectively extracted from the inpatients' administrative database of the Sicilian Regional Health System (RHS) at two time points: in 2019 (pre-intervention) and in 2022 (post-intervention). The RHS includes different anonymous healthcare administrative databases, which can be linked with each other at patient level by a univocal key. Thus, according to the International Classification of Deceases, 9th revision, Clinical Modification (ICD-9-CM) (25), data set will include all hospital discharge records of patients older than 18 years and younger than 100 years with a primary diagnosis of AMI (ICD-9-CM codes 410.xx), or patients older than 34 years and younger than 100 years with a primary diagnosis of ischemic stroke (ICD-9-CM codes 433.x1, 434.x1, 436). Admissions lasting < 2 days with a discharged home will be excluded, as well as hospitalizations of not Italian residents, transfers from another hospital with same diagnostic code, and admission preceded by discharge with diagnosis of AMI in the previous 4 weeks (ICD-9-CM codes 410.xx), or stroke in the previous 1 year (ICD-9-CM codes 430, 431, 432.x, 433.x1, 434.x1, 436). On the contrary, data in the rehabilitative setting will be extracted from the hospital administrative database, in addition to documental audits performed on inpatient medical records. Data set will include all hospital discharge records of patients older than 34 years and younger than 100 years with a secondary diagnosis of ischemic stroke (ICD-9-CM codes 433.x1, 434.x1, 436), and a primary diagnosis among the following: sequelae of cerebrovascular diseases (ICD-9-CM codes 438.xx), hemiplegia (ICD-9-CM codes 342.xx), other paralytic syndromes (ICD-9-CM codes 344.xx), dysphagia (ICD-9-CM Code 787.2), and other functional diagnoses (ICD-9-CM codes 781.0, 781.2). Admissions lasting < 2 days with a discharged home will be excluded, as well as hospitalizations of not Italian residents, admissions preceded in the last 1 year by another rehabilitative hospitalization for ischemic stroke, and hospitalizations with diagnosis of hemorrhagic stroke (ICD-9-CM codes 430, 431, 432.x).

Quality indicators

The intervention to be effective should be supported by a monitoring process of specific indicators of changes. Thus, the audit focuses on various QIs measured in terms of structures, processes, or outcomes of care. For the EASY-NET project, a set of suitable indicators has been selected, differing for healthcare setting. Indeed, in the emergency setting only indicators whose calculation is exclusively based on the administrative RHS database will be used, whereas in the rehabilitation setting indicators whose calculation is based on *ad hoc* hospital data collection (e.g., information recorded within patients' medical records) will be used.

A total of 18 indicators (i.e., 12 for AMI and 6 for ischemic stroke) were included in the set of emergency quality indicators (EQIs) for the EASY-NET Audit, 12 of which originate from the PNE, a national program acting to support clinical and organizational audits (3). These EQIs concerned three different periods, namely, (i) hospital admission (ii) 0–30 days from the admission, and (iii) 1 year from the admission. The first 30 days can be considered as the acute management of the disease, when the patient should receive most of the guideline-based therapies and rehospitalizations may be strongly linked to the index admission; 1-year rehospitalization after the acute phase (i.e., from days 31 to 365), besides primary care it should also depend on community support provided to patients.

A total of seven indicators were included in the set of rehabilitation quality indicators (RQIs) for the EASY-NET Audit. Five out of seven RQIs were outcome indicators, such as the number of hospital admission, the average number of days for admission to inpatient rehabilitation, and the type of discharge, whereas two assess the average recovery due to rehabilitation during hospitalization.

Further outcomes

For the EASY-NET project, process outcomes included a post-feedback survey.

The survey collects information in three sections:

- Items on demographic about the respondents.
- Items on perceptions of the feedback report, including whether the respondents reviewed it, whether the feedback is understandable and engaging, relevant to practice, presented in a form that can be used to influence practice, and whether the process of report delivery is appropriately timed and the report is readily accessible.
- Items on intent to change behavior, including whether and how the respondents used the feedback report to change their practice.

Statistical analysis

Descriptive statistics will be calculated for all variable targets. Continuous variables will be expressed as mean ± standard deviation, whereas categorical variables in frequencies and percentages. Student's t-test will be used to compare means, and the chi-squared test to compare proportions.

To assess whether the feedback intervention will lead to greater improvements in the "treatment group" vs. the "control group," difference in differences models and multilevel models will be carried out, adjusting for multiple covariates at baseline. No interim analyses are planned. Subgroup analyses will be performed on individual hospitals.

TABLE 2 Timelines of the EASY-NET WP7 project.

Procedure task	Months
Definition of the emergency quality indicators' (EQIs) and Rehabilitation quality indicators' (RQIs) protocol. Definition of the new A&F intervention	Apr 2019–Sep 2019
Hospital's recruitment and group's assignment	Oct 2019–Jan 2020
Audit: calculation of EQIs and RQIs at baseline	Feb 2020–Apr 2020
Staff training to perform the feedback intervention	May 2020
Realization of the feedback interventions	Jun 2020–May 2021
Re-Audit: calculation of EQIs and RQIs at follow-up	Jun 2021–Aug 2021
Statistical analysis	Sep 2021–Dec 2021
Results dissemination	Jan 2022–Mar 2022

Statistical analysis will be performed by using the open-source software R version 4.0.5. A $p < 0.05$ will be considered statistically significant.

Study status

Data collection commenced on 15 April 2019 and will be completed on 15 August 2023. The timelines of the initial project are reported in Table 2. Indeed, the project duration is of 36 months, but it has obtained an extension for the end of the activities.

Discussion

There is evidence of a significant gap between the quality and safety of care that patients overall receive and the recommended standards.

The written definition of the responsibilities and tasks for the members of the medical team, the use of checklists, an effective communication in the medical team, and the patient feedback are important parts of the quality control and risk management in order to improve the patient safety. However, it has been seen that such actions are often missing in many clinical settings (26).

The A&F interventions are recognized as part of a strategy for improving performance and supporting quality and safety in healthcare systems.

To the best of our knowledge, this is the first project of A&F performed in Southern Italy and the first project nationwide that implemented an A&F intervention in rehabilitative settings, where effectiveness studies are limited. Indeed, it is not common practice to carry out A&F activities in Sicilian hospitals. Consequently, it was considered appropriate to choose indicators comparable with national reference targets, at least in the emergency setting. In addition, this is the first study that experiences a psychologist's intervention and the use of

remote information and communication technologies typical of telemedicine.

Despite widespread use of A&F in healthcare systems as a strategy for quality improvement, uncertainties remain about its effectiveness (10). This could be related to variability of the interventions that do not always take into account human factor aspects (communication, leadership and followership, team working), which, in addition to the technical ones, are the key to building quality and reliability in healthcare. The new model of A&F requires a change in the preparation and delivery of the entire feedback process. Systematic observation and analysis of technical and non-technical skills components in the new format for clinical audit will turn an administrative review process into a highly educational experience that people are looking for.

We believe that a psychological model that supports A&F throughout its journey can improve the quality of work choices and the work environment itself. Indeed, the conceptual theory of psychosocial safety climate (PSC is based on the perspectives of occupational stress, psychosocial risk, and organizational climate literature (27). PSC is a specific component of organizational climate related to freedom from psychological harm at work (28). It reflects management's commitment to the psychological health of employees and the priority they give to safeguarding psychological health over production needs. Like organizational climate, PSC is conceptualized as a property of the organization, consisting of the aggregate perceptions of individuals within the organization regarding management's commitment to protecting their psychological health and safety (28). The PSC construct is largely derived from the idea that individuals ascribe meaning to their work environment.

In addition, many studies in the literature have highlighted how problems at work affect the development of mental health issues. Phenomena such as stress, bullying, and burnout are major contributors to a job done poorly (29). Indeed, acting on adaptive strategies, such as coping, dysfunctional phenomena that affect mental health can be prevented. Therefore, we hypothesized that even in the A&F model working on motivational and adaptive levels can significantly affect the care pathways. Therefore, more assurance could be given to healthcare workers and consequently provide better service to users/patients.

We expect that the new A&F model results in an overall improvement in the performance of healthcare providers and the quality and safety of care received by emergency and rehabilitation patients through behavior and action changes based on the development of critical thinking guided by the presence of the psychologist.

The COVID-19 pandemic determined a health emergency that impacted standard care processes. In this context, the A&F interventions may become a concrete tool able to support healthcare professionals in proactive actions aimed at reducing the risk associated with infection (30, 31). In

particular, the use of ICT could lead to major facilities in the procedure of A&E, such as the ones experimented in this project.

Limitations

The main limitation of this project is the recruitment and availability of healthcare professionals to receive the information for culture change. However, the A&F phase is carefully supervised and monitored by a central steering committee, which is responsible for identifying and training, each hospital, and the staff responsible for conducting the audits.

In addition, in the absence of benchmarks (e.g., in the rehabilitation setting), there is a difficulty in defining appropriate RQIs to detect behavior change.

Ethics statement

As the study did not directly involve patients, data are retrospectively collected and extracted in aggregate form; this study did not require the approval of the Ethics Committee, in accordance with the current rules of our hospital. However, all target population of the A&F intervention will provide written informed consent to participate in the study. Results will be disseminated through journals and conferences, and will be particularly relevant for healthcare managers and clinicians intending to implement strategies for quality improvement based on an effective communication among different healthcare workers, as well as for researchers seeking to refine the structure and evaluate the effectiveness of such programs.

Author contributions

NA coordinated the development of the EASY-NET project. PB and RC coordinated the development of the WP7. MDM and MCDC designed the study, designed the hospitals' stratification and the QIs protocol. PB, RC, MCDC, and FC designed the new A&F model. RC, MCDC, and FC drafted the manuscript. FC designed both the training and therapeutic intervention for effective communication. NA and PB critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

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China's "dynamic clearing" epidemic prevention policy: Achievements, challenges, and prospects

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The COVID-19 outbreak makes up a major public health emergency, and each country has adopted different epidemic prevention policies and measures. Since the control of COVID-19 in 2020, China has gradually developed a "Dynamic Clearing" epidemic prevention policy of "external input prevention and internal rebound prevention". The policy has been effective in protecting people's lives and health and developing the country's economy as much as possible, but it has also faced some challenges, such as slowing economic development, huge prevention, and control costs, and expanding secondary disasters and risks. Reviewing China's current "dynamic clearing" policy, it is still the overall policy to continuously improve guiding policies, construct scientific prevention measures, and promote digital governance at the grassroots level.

Digital governance

It has been over 2 years since the outbreak of COVID-19 occurred, and the epidemic still shows no signs of abating. In particular, since March 2022, concentrated outbreaks have occurred in several Chinese cities such as Qingdao, Weihai, Jilin, Changchun, Shenyang, Shanghai, Guangzhou, Chengdu, Beijing, and so on, with 534, 8,157 confirmed cases and 24,034 cumulative deaths reported nationwide as of 16:00 on 8 August (1, 2). In Shanghai, in particular, since the beginning of March, the epidemic has become more and more serious. On 1 April, a region-wide standstill began, with traffic and supply chains blocked until 16 May, when it was gradually lifted, and on 1 June, normal production and living order was fully restored, and regular management of the epidemic prevention and control was implemented. As the largest city in China and the third-largest in the world, with a population of more than 27 million, it plays a pivotal role in China's economic development. In 2021, Shanghai's total economic output ranked 10th among the country's 31 provinces and cities, and the sealing control in the past 2 months has had a profound impact on the economy of Shanghai and China.

Faced with this major public health emergency, China has been adopting the "external prevention of importation and internal prevention of rebound" approach after the battle against the epidemic in Wuhan at the beginning of 2020, and although there have been sporadic occurrences, they have been promptly and effectively controlled and have had little impact. On December 11, 2021, the National Health Commission formally proposed "dynamic clearing" as

the general policy for the prevention and control of epidemics in China. On 5 March 2022, in the Fifth Session of the 13th National People's Congress, He Lifeng, chairperson of the National Development and Reform Commission, presented the Report on implementing the National Economic and Social Development Plan for 2021 and the Draft National Economic and Social Development Plan for 2022, also proposed the general policy and guideline of "dynamic clearing" for epidemic prevention, which was hotly debated by the delegates of the National People's Congress. According to an article entitled "Why the world needs China's dynamic clearing policy" published on the Bloomberg website on 9 February this year, China's "dynamic clearing policy" has benefited the world. The Wall Street Journal website also published an article on 16 February entitled "China's new "dynamic clearing" policy on infections contains lessons for other countries," stating that China's "dynamic clearing" anti-epidemic policy has achieved what every country was seeking for 2 years: low death rate and as little economic disruption as possible (3). On March 17, General Secretary Xi Jinping chaired a meeting of the Standing Committee of the Central Political Bureau, stressing that "we should always adhere to the supremacy of the people and life, adhere to scientific precision and dynamic clearance, and curb the momentum of the spread of the epidemic as soon as possible," further showing the direction for the prevention and control of the epidemic (4). During his visit to Hainan on April 10–13, Xi Jinping once again stressed the importance of "adhering to scientific precision and dynamic clearing" (5). Therefore, the policy of "prevention of external importation and internal rebound" under the general policy of "dynamic clearing" is still the basic platform and guideline for future epidemic prevention work.

Liang Wannian, head of the expert group of the National Health and Wellness Commission's Leading Group for Epidemic Response and Disposal, introduced the so-called dynamic clearing, which includes three aspects: the first is the timely and proactive detection of sources of infection. The sources of infection include patients, asymptomatic infected people, and other animals that may carry pathogens. The main means of detecting the sources of infection are through monitoring early warnings at fever clinics and some tests and active screening. Second, when a case is detected, public health and social interventions are quickly taken, including control of the outbreak site, the management of close contacts, epidemiological investigation, and control measures to reduce crowd gathering. Third, effective treatment, mainly using a combination of Chinese and Western medicine and other methods, to effectively treat patients, stop the progress of the epidemic as soon as possible and far, prevent light from becoming serious, and reduce the occurrence of serious illness and death. Liang Wannian stressed that the general policy of "dynamic Clearing" is to pursue the greatest possible integration of socioeconomic development and epidemic prevention and

TABLE 1 Confirmed cases and deaths of new coronary pneumonia worldwide, USA and China.

	Cumulative number of confirmed cases of new coronary pneumonia	Cumulative new coronary pneumonia deaths
Worldwide	528670960	6303059
United States	85145035	1029269
China	2114305	161515

TABLE 2 Global ranking of excess deaths from new coronary pneumonia in 194 countries.

Rank	Name of the country	Excess deaths in New coronary pneumonia
1	India	4740894
2	Russia	1072326
3	Indonesia	1028565
4	United States	932458
5	Brazil	681267
……	……	……
193	Japan	−19471
194	China	−52063

control. The "dynamic clearing" approach requires speed and precision, and the rapid elimination of outbreaks when cases are detected (6).

Over the past 2 years since the outbreak of COVID-19, China has provided the world with a uniquely Chinese experience and solution to combat the epidemic, which is the "dynamic clearing" policy of "prevention of external importation and internal rebound." The outstanding achievements of this epidemic prevention policy are 2–fold.

First, it has protected the lives and health of the people. The Communist Party of China has always put "people first, life first" as its governing philosophy. China has withstood round after round of epidemics and dealt with dozens of localized epidemics quickly and effectively, protecting people's lives and health to the maximum extent possible. As of 6:30 p.m. Beijing times on May 25, 2022, there were 52,867,060 confirmed cases of NCCP and 630,059 deaths worldwide. In the United States, there were 85,145,035 cumulative confirmed cases of NCCP and 1,029,269 cumulative deaths (7), see Table 1.

According to the WHO's ranking of 194 countries or territories worldwide in terms of data on number of excess new crown deaths, the top five countries are India, Russia, Indonesia, the United States, and Brazil, with a death toll of 4740894; 1072326, 1028565, 932458, and 681 1,267, respectively. The country with the lowest number of deaths was China, ranked 194th, followed by Japan (8), see Table 2.

TABLE 3 Ranking of excess deaths from new coronary pneumonia by country.

Rank	Name of the country	Deaths (10,000)
1	India	410
2	United States	110
3	Russia	110
4	Mexico	79.8
5	Brazil	79.2
6	Indonesia	73.6
7	Pakistan	66.4

TABLE 4 Summary of the direct costs of shanghai seal control.

	Government/ Aid (parity)	Residents (rush price)	Total (RMB billion)
Subsistence expenditure	100	300	400
Expenditure on nucleic acid/antigen tests	78		78
Square cabin hospital construction/renovation expenditures	150		150
Community volunteer allowance expenditure	331		331
Roadblocks and other expenses	33		33

However, according to a paper published in The Lancet in March 2022, *Estimating excess mortality because of the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21* (9) reveals that while the official number of deaths recorded for the period 1 January 2020 to 31 December 2021 is 5.9 million, the new study estimates that 18.2 million additional deaths (excess deaths) occurred during the same period. On the country level, the highest estimated excess deaths are in India (4.1 million), the United States (1.1 million), Russia (1.1 million), Mexico (798,000), Brazil (792,000), and Indonesia (736,000), and Pakistan (664,000), see Table 3.

A new concept invoked by the WHO here is that of "excess mortality", which refers to the difference between the number of recorded deaths from all causes and the number of deaths expected based on past trends, it is a key indicator of the true number of deaths in a pandemic. Various studies have shown that geographical location, population density, demographics, prosperity, etc. can all influence excess mortality (10–14).

We can argue that regardless of the data published by either party, the number of deaths in China in the COVID-19 is tiny and the rate is low. From this perspective, China is focusing on protecting people's lives and health in its epidemic prevention.

The dynamic clearance effectively safeguards sustained and stable economic development. The key to determining the best solution to combat the epidemic lies in how to contain it in a shorter period at a lower cost, reduce the adverse impact brought about by the epidemic, and ensure sustained healthy and stable economic and social development with good prevention and control results. In 2020, China will be "the first to control the epidemic," "the first to resume production" and "the first to turn economic growth from negative to positive." In 2021, GDP will grow by 8.1% compared to the previous year, with an average growth rate of 5.1% over the next two years, making it one of the fastest-growing economies in the world. China has stabilized its supply chain in 2020 and 2021, maximizing the smooth flow of the supply chain; stabilizing the industrial chain, enabling the rapid recovery and stable development of the Chinese economy; and stabilizing consumer confidence,

creating favorable conditions for the market to maintain long-term stability (15).

However, it should also be noted that China's "dynamic clearing" disease prevention policy also faces serious challenges.

First, the economic growth situation is not optimistic. The central government has established an expected growth target of around 5.5% for the entire year of 2022 in China. The epidemic affected the economy, by 4.8% year-on-year in the first quarter of this year, a large distance from the expected target. In April, the value-added of industries above the national scale fell by 2.9% year on year. The national services production index fell by 6.1% year-on-year in April. Total retail sales of consumer goods fell by 11.1% year on year to RMB2, 948.3 billion in April. Fixed asset investment (excluding farm households) fell by 0.82% in April from a year earlier. Influenced by the intensifying downward pressure on the economy, the urban survey unemployment rate continued to climb in April, reaching 6.1%, widening the gap with the expected target of 5.5% or less for the year. Among them, the survey unemployment rate for the population aged 16–24 climbed to 18.2% (16).

Second, the cost of epidemic prevention continues to increase. New coronavirus mutations are more deeply hidden and spread quickly, making prevention difficult. Some economists have calculated the cost of prevention and control in Shanghai from April 1st to May 22nd.

The direct cost of the 52 days was RMB 99.2 billion, or RMB 1.907 billion per days on average, from April 1, when the official announcement was made that the entire area would be under static management, to May 22, when some bus lines resumed operation. The implicit (indirect) cost test result was $3.97 trillion, or an average of $76.3 billion per days. The direct and implicit costs add up to RMB 4.07 trillion, which is close to the annual GDP of Shanghai in 2021 (RMB 4.32 trillion) (17). See Tables 4, 5.

Apart from Shanghai, in other cities in China such as Beijing, Guangzhou, Changchun, Shenyang, and other cities

TABLE 5 Summary of hidden (Indirect) costs of shanghai sealing control (RMB billion).

Rent, utilities, and gas costs	1,021
Nucleic acid waiting for costs	1,348
Loss of industrial output	1,473
Loss of market capitalization of securities markets	35,700
Secondary hazards and others	147
Total	39,689

where epidemics have occurred, the costs of prevention and control are enormous. The costs of prevention and control will continue to increase, putting enormous financial pressure on local governments at all levels.

Third, secondary disasters and risks have expanded. In some places, in order to cut off the source of transmission and prevent the spread of the epidemic, simple and violent methods such as road blocking and road digging were adopted to control the movement of people, which affected people's normal travel and life and was not conducive to scientific epidemic prevention and control; the public refuses to seek medical attention for fear of cross-infection and resorts to self-isolation at home instead of going to the hospital, allowing family members to infect each other and leading to an increase in family clusters of cases; some local hospitals have adopted a one-size-fits-all approach, treating only patients with COVID-19 and neglecting the needs of other patients, resulting in many non-COVID-19 patients not receiving timely treatment; some residents go out without protective gear, leading to an increased chance of transmission; Sometimes, the improper use of protective equipment for epidemic control has led to a high number of accidents. We should give these secondary disasters arising from epidemic control sufficient attention.

Although there are indeed serious challenges to the "dynamic clearing" epidemic prevention policy, there is still a need to take stock of past epidemic prevention experiences, reflect on the current epidemic prevention policy and its implementation measures, and promote the scientific of China's epidemic prevention measures.

First, the "dynamic clearing" epidemic prevention policy should be further improved. The National Health Commission, as China's public health authority, should convene experts from various fields, including clinical medicine, law, public health management, immunology, etc., to conduct scientific discussions and ensure the scientific and rational nature of the policy. The basic guiding principle is that on the premise of adhering to the general policy of "dynamic clearing," some localities can explore and summarize some good experiences and practices according to the local epidemic situation and characteristics, to further improve the scientific and precise level of epidemic prevention and control, and strive to achieve the maximum prevention and control effect with the minimum cost.

Second, vaccination should be strengthened, especially for the elderly and children. According to the mortality rates in various countries, the elderly and children are the biggest victims of the epidemic, as their immunity is low, their organs are declining and aging, and children's organs are underdeveloped. The vaccination rates in China is currently 88.64%, but the rate for the elderly is only 81.49% (2). The need to further increase the vaccination rate for the whole population as well as the full vaccination rate is a fundamental measure to prevent the attack of the new coronavirus.

Thirdly, we should promote the science of epidemic prevention and control measures. China has a vast territory, and we must not apply prevention and control measures across the board. We must firmly prevent and avoid the tendency to "relax prevention and control" and "over-prevention and control." Because of the new characteristics of Omicron, we should further strengthen containment, management, and control, shorten the time of centralized isolation, and implement categorized treatment. Only by targeting and scientifically and precisely preventing the epidemic can we achieve the greatest effectiveness in prevention and control at the least cost.

Fourth, it should promote the construction of digital government, especially to strengthen the digital governance of the grassroots' government. One of the major reasons for the many problems in the prevention and control of the Newcastle pneumonia epidemic in some areas in terms of epidemic risk warning, information collection, material deployment, and staff coordination is the lagging construction of digital government, insufficient application of digital technology, and the need to improve the efficiency of digital governance. Government departments at all levels should use digital technologies such as big data, artificial intelligence, and cloud computing to play a better supporting role in the epidemic (risk) monitoring and analysis, virus (crisis) tracing, prevention, control, and treatment, and resource deployment. In the fight's context against the epidemic, the government should speed up the reform of grassroots services, vigorously optimize the "Internet + government services," focus on matters that are frequently used by the public, and promote "one network for all" government services, so that the public can conduct business without having to leave home. The government will also focus on the maintenance and promotion of government service apps, so that they are not only usable but also useful, and strive to make "contactless services" a standardized work requirement so that the "palm of the hand" becomes a personal service for the masses. The mainstream service mode of government services.

Author contributions

Conceptualization and writing—review and editing: QW. Methodology: QW and LH. Formal analysis: LH. Writing—original draft preparation: LH. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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

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Vaccine acceptance in rural India: Engaging faith leaders as vaccine ambassadors

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Introduction: Religious faith is a key marker of identity and shapes community perspectives and trust. Faith leader involvement in vaccine campaigns in India have been beneficial to counter misinformation regarding infectious diseases such as polio. Faith leaders are influential stakeholders who bear potential to enhance public confidence in vaccine campaigns.

Context: While vaccine coverage has been increasing in India, inequities abound, especially in populations with historically low vaccine confidence. The COVID-19 pandemic has led to major disruptions in delivery of routine immunization services for children. To address these challenges, we co-designed interventions aimed at contextual communication strategies and peer support. Engaging faith leaders was an important part of this intervention. In this report we describe our experience and highlight the perspectives of faith leaders and their expectations of the outcomes for this intervention.

Programmatic elements: The CIVIC Project, conducted from January to December 2021 aimed to engage caregivers, community health workers and key stakeholders, particularly, faith leaders in co-designing interventions to address vaccine hesitancy in Mewat. The project, deeply rooted in community based participatory research, used a three-E approach (Exploration of community perspectives, Establishment of vaccine trust and awareness, Engagement in vaccine promotion activities) to successfully engage faith leaders in the design and dissemination of media messages advocating for vaccine acceptance and uptake.

Lessons learned: The involvement of faith leaders in the intervention benefited the community in two ways. First, faith leaders were spotlighted *via* videos, often disseminating advice and personal anecdotes about vaccines, thus reassuring caregivers and community members who previously expressed distrust in vaccines. Second, involvement of trusted faith leaders provided a platform for a two-way dialogue for the community to openly discuss and address myths and misconceptions regarding vaccines. This project provided

the learning that co-creating interventions with faith leaders who are often gatekeepers of close-knit communities can lead to the development of vaccine positive messaging that community members relate with, motivating increased vaccine confidence.

Introduction: The role of faith and faith leaders in health promotion programs

Religious faith represents a key social and environmental driver that can influence an individual's beliefs, their health behavior, and practices (1). Health promotion programs rooted in the involvement of faith-based organizations and in the engagement of faith leaders as advocates for disease prevention and treatment have proven effective in bringing about positive change in community health (1).

In 2019, the World Health Organization (WHO) identified vaccine hesitancy among the 10 threats to global health (2). Vaccine hesitancy has become inextricably linked to religious faith in several ethnic communities across the globe. Concerns about vaccine safety combined with circulation of misinformation poses severe threats to public health and attainment of herd immunity against infectious diseases (3). Addressing vaccine hesitancy through multi sectoral partnerships and facilitating faith-based dialogues is imperative to drive acceptance and uptake of COVID-19 vaccines (4).

Historically, communication strategies centered around faith leaders have led to favorable outcomes in tackling misinformation and reducing the spread of infectious diseases, including poliomyelitis (polio), human immunodeficiency virus (HIV), and Ebola (5). Evidence from polio eradication efforts in India and Pakistan shows that minority Muslim communities were among the hardest to reach. Low polio vaccine uptake was linked to vaccine hesitancy and misinformation among community members. In these settings, participation of faith leaders in polio campaigns enhanced public confidence and bolstered the credibility of the Polio Eradication Initiative leading to an increase in vaccine coverage (5).

In India, the UNICEF-managed Social Mobilization Network (SmNet) specifically countered religious vaccine refusals by approaching faith leaders to speak about the impact of polio during Friday prayers and regularly make mosque announcements (6). Building off the successful elimination of polio in India, the involvement of faith-based leaders and grassroots-level involvement in immunization efforts was expanded to promote routine immunization services, sanitation, and other maternal and child health programs in India (7, 8).

Context: Addressing gaps and challenges for vaccine acceptance in Mewat, Haryana

India is currently tackling pockets of populations unwilling to receive or unaware of COVID-19 vaccines (9). Additionally, the COVID-19 pandemic caused major disruptions in routine immunization services for children in India leading to significant declines in coverage rates, particularly during lockdown periods. This left high numbers of children susceptible to vaccine-preventable diseases (10, 11).

In the Mewat district of Haryana State in India, low rates of vaccine coverage have been a long-standing obstacle to health improvement. According to data from the National Family Health Survey (NFHS-5, 2019), 53.8% of children between the ages of 12–23 months were reported to be fully vaccinated with bacille Calmette-Guerin (BCG), measles, and three doses each of polio and diphtheria, pertussis, and tetanus (DPT) vaccines (12, 13). This value lags far behind the national average of 76.4% (14) and falls short of the WHO goal of reaching 80% coverage for all vaccines in national programs for every district as per the Global Vaccine Action Plan (15).

Previous research exploring community perceptions of vaccination in Mewat has highlighted several factors that limit vaccine acceptance, such as fear of side effects, low education levels, poor communication with CHWs and religious factors (16). To increase vaccine uptake and address barriers to vaccination, it is essential to gain a deeper understanding of nuanced community-level factors driving vaccine hesitancy, along with identifying trusted sources for decision-making (16, 17). Faith leaders are often considered one such trusted source in the community, as they influence health behavior across individual and socio-cultural levels (18). Faith leaders are members of the community who are recognized for their role in guiding and inspiring religious and faith-based beliefs and practices of the community, playing an authoritative and influential leadership role.

To meet the challenge of low vaccine uptake in this community, we revitalized social mobilization approaches involving faith leaders. This report highlights findings from the Community Health Worker-Led Intervention for Vaccine Information and Confidence (CIVIC) Project in a rural setting in India. Utilizing a combination of broadcast, print, and social media sources to disseminate vaccine messaging from faith leaders led to improvements in community-level vaccine awareness and acceptance (19). As faith leaders represent a key resource in building vaccine confidence in the community, we explored their perspectives regarding vaccines and engaged them to partner with local health workers in promoting messages of best practices with regard to vaccines.

Methods

The CIVIC Project was conducted from January to December 2021. The project was designed using a community based participatory research approach, seeking active collaboration from the community members in Mewat in the intervention design. This study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (IRB) under IRB submission number 14670/CR717. The IRB determined that proposed activities were exempt under category 2. Under this exemption, the inclusion of participants in our study is identifier recorded and not sensitive. This implies that any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.

The interventions for the project were co-designed by the research team and community iteratively. This strategy was used to strengthen the decision-making power of community members, learn from their problem-solving skills and to ensure that the interventions would be tailored to the specific needs of the population.

The intervention with regard to faith leaders consisted of a three-E approach:

1. Exploration of community perspectives
2. Establishment of vaccine trust
3. Engagement in vaccine promotion activities.

Exploration of community perspectives

The project was initiated with a series of formative interviews (consisting of open and close ended questions) conducted with 10 community members and 10 community health workers (CHWs). Community members recruited for the interviews were involved in a variety of occupations including teaching, social work, farming, and involvement in the panchayat (village council). These formative interviews were followed by two virtual human centered design (HCD) workshops conducted with both these groups (community members and CHWs). These formative interviews and HCD workshops were aimed at understanding community perspectives regarding vaccines and identifying specific barriers to vaccine acceptance that could be addressed through the project (20). The interviews and HCD workshops were facilitated by data collectors who had experience with qualitative data collection. Data collectors were provided with additional training on specific qualitative techniques such as probing and open-ended questions.

Two independent readers conducted rapid qualitative evaluation and thematic analysis on interview responses and documentation from the HCD workshops. The preliminary data from these interviews and HCD workshops overwhelmingly indicated that faith leaders were one of the most trusted sources of information in the community. This suggested that their involvement in multiple aspects of the intervention would be pivotal for improving vaccine uptake and acceptance in the community.

To facilitate faith leaders' involvement in the intervention, the research team approached 10 faith leaders in the area. Through the research teams prior work in Mewat, these faith leaders were identified through purposive sampling. Our sampling strategy enabled us to identify faith leaders who had an established reach and spanning across diverse sections of the community who were well-positioned to provide insights on their individual and broader community perspectives about vaccines. Initial conversations revealed that the faith leaders themselves had several doubts and questions about vaccines due to gaps in their own awareness about the diseases prevented by vaccination and the overall health benefits of vaccines. Until these were addressed, they were hesitant to promote vaccines among their communities.

Establishment of vaccine trust and awareness among faith leaders

To address faith leader concerns regarding vaccines and boost their confidence with advocating for their uptake in the community, the research team facilitated a series of discussions and feedback with the faith leaders spanning a 6-month period (January–July 2021). The two approaches used to connect with the faith leaders and build their trust were knowledge-sharing and enabling interactions with healthcare providers.

Informal knowledge sharing sessions

The research team frequently met with faith leaders to provide them with information about the project and establish

a sense of comfort and familiarity between health providers and the faith leaders. During these meetings, the research team encouraged the faith leaders to share their doubts and questions about vaccines. These sessions were planned to be small in numbers (2–3 faith leaders at a time) and informal. Further, the research team made a deliberate effort to be receptive to the faith leaders' questions.

These sessions provided the faith leaders with an opportunity to share their doubts in a safe environment, ensured their concerns were appropriately addressed, and facilitated trust across multiple levels of the community. Maintaining continuous dialogue with faith leaders led to the gradual establishment of trust and dispelling of rumors.

Interactions between healthcare workers and faith leaders

While the informal sessions reassured the faith leaders of the positive impact of vaccines on child health outcomes and long-term community health, they were unclear about the issues related to vaccine delivery and unsure of how their involvement could benefit vaccine acceptance. Therefore, the research team facilitated interactions between faith leaders, CHWs and other health professionals, including representatives from polio campaigns.

Community health workers are often women who are from communities they serve in and perform a range of tasks for health promotion and prevention [21, 22]. As they have been responsible for sustaining routine immunization services during the pandemic in addition to supporting COVID-19 vaccine drives, CHWs provided insight to the faith leaders on their struggles with combating multiple sources of vaccine hesitancy in their community. Additionally, evidence shows that faith leaders played a major role in polio eradication in India through countering faith-based hesitancy by enhancing community engagement, especially among hesitant populations in Uttar Pradesh, a neighboring state to Haryana [6]. Interactions with representatives from the polio campaigns enabled the faith leaders to learn more about these success stories, making them keen to actively participate in the CIVIC project.

The combined approaches of informal knowledge sharing with the research team and interactions with healthcare workers provided the faith leaders with a comprehensive understanding of the benefits that increased vaccine acceptance and uptake would offer to the community. The informal sessions were critical in enabling the faith leaders to comfortably share their concerns. This was complemented by the interactions with the health care workers through which the faith leaders gained knowledge about vaccines delivery and the challenges faced by the healthcare workers during their interactions with the community.

Engagement in vaccine promotion activities

The interactive sessions for the faith leaders with the research team, CHWs and other health workers set up a strong rapport between the faith leaders and the research term. Collaboratively, they designed activities that would provide platforms for the faith leaders to provide information about vaccines to the community in a manner that would ensure reach to the community despite social distancing norms and in the absence of community gatherings. The two key activities included use of messaging in popular media, and participation in the Community Accountability Board (CAB). Faith leaders were not offered any financial or other incentives to participate in these activities. They co-designed and came forth to volunteer their time and participation in these activities because of their gradually established conviction of the benefits that positive vaccine messaging would offer to their communities.

Media messages

Faith leaders, along with other trusted community members (teachers, social workers) spoke in short video messages in which they advocated for vaccines. In these videos, faith leaders spoke about the importance of vaccinating children and shared potential negative long-term impacts of children remaining unvaccinated. These context-specific videos were tailored to the needs of the community and used local vernacular to ensure their message was heard and understood. These short videos were leveraged by CHWs in door-to-door communications with caregivers, and they were shared extensively across social media platforms in Mewat. Of these platforms, WhatsApp was a particularly popular mode of circulating this video. The messages from these videos were also discussed over broadcasting media channels such as the local station Radio Mewat which has been an important awareness building platform for this community for several decades [23]. Further, print articles highlighting these messages and the CIVIC project, were published in five local news outlets spanning English, Hindi and Urdu language papers. This multi-pronged dissemination enhanced the reach of messages supporting the value of vaccines for community health.

Involvement in community accountability board (CAB)

Observing the positive impact of the videos, the faith leaders agreed to be members of the CIVIC Project's Community Accountability Board (CAB). This CAB of influential community leaders met virtually *via* video conferencing platforms every month to discuss progress of the CIVIC Project, make changes to the project's intervention aspects as needed by the community, and discuss other health issues in Mewat.

Given the instrumental role of their endorsement and messages in shaping community perspectives, the faith leaders' decision to join the CIVIC Project's CAB was monumental. The CAB consisted of 10 members, with one Hindu faith leader and two Muslim faith leaders (Maulanas). Through engagement in monthly meetings, the CAB offered a platform for the faith leaders to continue to partake in regular discussions and decisions regarding COVID-19 vaccination and routine immunization uptake in the community. Their engagement in CAB meetings enabled them to share concerns, perspectives or misconceptions observed from their congregations, as well as identify effective means to address these with other CAB members. The involvement of faith leaders in the CAB, as well as other aspects of the intervention, facilitated unprecedented trust in vaccination in Mewat.

Along with being a platform to bring together the faith leaders with other members of the community, the CAB meetings were used as a means for our research team to connect with the community to obtain their thoughts on the project interventions. These monthly CAB meetings were recorded with along with extensive field notes maintained by the research staff to document these meetings. Two independent readers conducted rapid qualitative evaluation and thematic analysis of the data from each of the monthly CAB meetings to understand the impact of the intervention on the community.

Results

The CIVIC project attempted to use a comprehensive and nuanced approach by involving faith leaders throughout the duration of the project, enabling them to play an active role in the intervention design. Not only did we encourage them to participate in advocacy efforts, we aimed to thoroughly understand their perceptions and provide them with a space to discuss concerns. As a result, we were able to gain their trust and earn their willingness to be advocates for vaccines. This comprehensive approach proved to be impactful in two diverse ways: first, through enhancing the community members' trust and acceptance in vaccines, and second, by supporting community health workers in their communications with caregivers.

Community members who expressed distrust in vaccines and were skeptical about the potential side effects felt reassured by seeing a faith leader they recognized and respected support vaccines. The video disseminated *via* social media was helpful in motivating the mothers, their husbands, and their families to understand the benefits vaccines offer for their health and for their child. Caregivers themselves also noted the positive impact of this video:

If our Maulana is asking to get the vaccination and also saying that the vaccines are good, then I will definitely get my [pregnant] wife vaccinated. And I will also get the child, which is to be born, fully vaccinated. (Husband of pregnant woman)

The faith leader videos also served as a helpful supplement for CHWs to improve their communication with caregivers regarding vaccines. Leveraging WhatsApp to share videos of faith leaders advocating for vaccination aided their communications with caregivers, inspiring willingness to receive vaccines for themselves and their children.

The religious leader video has been a very useful aspect of the intervention. During talks with the caregiver, I have shown these videos while communicating about vaccination then they suddenly made a decision for [accepting a] vaccine. (Community Health Worker)

Discussion

As evidenced by our preliminary conversations with community members, faith leaders are valued members of the community members in Mewat, whose opinions are held in high regard.

Although previous projects have involved faith leaders, including The Pulse Polio Immunization program in India, these approaches were designed to involve the faith leaders in advocating for vaccines. All engagement activities began with the goal of understanding the "underlying reasons for the resistance" to the polio program, and, at this point, key faith leaders who could be involved in the polio program were identified. However, the program results were not encouraging, as faith leaders still felt a high degree of misapprehension about polio vaccines (6).

Our results show that it is essential to involve faith leaders in a sensitive, consistent, and long-term manner. Their comprehensive role in not only the advocacy efforts but also in the formative research, design and dissemination of interventions, and follow-up activities to improve vaccination proved to be a fruitful investment in our project and may be impactful in future work. Additionally,, the creation and involvement of faith leaders in the CAB meetings provides a long-term platform for community members and faith leaders to continue to meet and engage on vaccine and other health related issues beyond the duration of the project. These CAB meetings developing community accountability and ensuring long term sustainability of these interventions.

Globally, faith leaders have played a dynamic role in the COVID-19 response and have supported their communities to overcome vaccine hesitancy (24, 25). Even prior to the pandemic, faith leaders were recognized as capable of organizing and cultivating community participation in health issues (18).

Amplifying their broad involvement by understanding their concerns, earning their trust, and then empowering them to use their voices to improve vaccine-seeking behaviors in communities has the potential to increase COVID-19 vaccine uptake and stimulate lasting trust in vaccines. In India, studies have shown that "hot spots" of negative or unclear information on COVID-19 vaccination can be addressed by involving friendly organizations who can clear strong disbeliefs (26). Faith leaders often gatekeepers of their communities and our results show that they can be powerful agents of change to facilitate vaccine confidence among hesitant communities.

Recognizing the unique position of faith leaders in communities, India's Ministry of Health and Family Welfare's COVID-19 Vaccine Communication strategy has highlighted their involvement as a key component of the vaccine advocacy strategy (27). This communication strategy from the Indian government recommends faith leader involvement in social mobilization activities and organizing advocacy events with faith leaders and faith-based institutions, complemented with written appeals and audio/video bytes for mass social media dissemination (27). However, to ensure long term sustainability, it is important for the interventions to be context specific and feasible with resources accessible to the community. Creating nuanced interventions that take into account community-specific hesitations, and work with faith leaders as vaccine advocates, is a critical grassroots-level strategy to improving vaccine acceptance across India.

Exploring which community influencers are most critical across different settings and employing "bottom-up" approaches to partner with communities to design interventions may help enhance trust and address inequities in a targeted manner (28, 29). The CAB brought together multiple stakeholders who play diverse roles in the community and were eager to share their thoughts and ideas for the improvement of their community's health and development. Toward the end of the project, the CAB felt that while progress had been made in terms of vaccination, they wanted to continue the meetings to discuss issues beyond vaccination to work toward improving broader issues in Mewat. Through their continued role in CAB, the faith leaders can bring the lens of religion, spirituality and faith to community discussions and decisions. This perspective is crucial to designing and implementing behavior change strategies that will resonate with the community and be sustained in the future (30).

In the past, faith leaders' involvement in health communication has led to favorable outcomes in tackling misinformation and reducing the spread of infectious diseases including polio, HIV and Ebola (4). Their involvement has proved to be crucial in global advocacy for polio vaccines, reducing stigma associated with HIV and changing religious practices associated with burials that were a source of Ebola exposure and infection. Working with individuals at all levels of community, particularly faith-based groups, has shown great

value in several health emergencies (5). Tailoring interventions to meet specific needs of communities is crucial to optimizing long-term success and promoting equity. As faith leaders in certain closed-knit communities such as Mewat play a large role in influencing community health behaviors, we involved them in co-creating interventions specific to the needs of the community. We have shown how innovative ways of involving faith leaders to facilitate the success of health promotion programs, particularly in the context of COVID-19 vaccine uptake and recovering from disruptions in routine immunization services in low-coverage areas, bears potential for positive outcomes (4).

Strengths and weaknesses of our approach

A unique strength of this project was that it was designed to be implemented completely virtually as a result of the COVID-19 pandemic. Despite the challenge of conducting community outreach in a rural setting without in-person meetings, performing project activities virtually enabled delivery of reliable vaccine messaging in a safe manner, adhering to movement restrictions and social distancing norms during the pandemic. This approach also allowed increased participation of community members and CHWs in the interventions, as they were able to join meetings from their homes without needing to travel long distances, limiting interference with their familial or professional responsibilities.

While our narratives in Mewat are descriptive of a small sample, our work suggests that the approach of involving faith leaders as champions for vaccines through dissemination of video messaging and involving them in decision making bodies was successful in promoting vaccine uptake and may be effective in similar areas of low vaccine uptake. However, a limitation of our work was voluntary response bias, as the study team could only engage with faith leaders who were willing to understand more about vaccines and engage in promotion activities. We were not able to access all the faith leaders across the community.

Lastly, the faith leaders involved in the project activities were all male. Going forward, exploring and enabling the involvement of women religious leaders in community decisions pertaining to health would be beneficial. Previous research has indicated that providing women with the opportunities to lead communities has been associated with higher educational attainment for girls, curbed negative attitudes toward female empowerment, and greater agency among women for decision making (31–33).

In this report, we have highlighted the process by which faith leaders' concerns about vaccines were understood and addressed, followed by their engagement in vaccine promotion

activities. We have also described the positive influence of these activities. To gather a deeper understanding of the impact of these interventions, we plan to undertake a systematic evaluation of these approaches in future research.

By supporting and guiding their non-traditional leadership, along with innovative and advanced modes of message delivery, we have shown how faith leaders can facilitate long-lasting strategies to improve vaccine acceptance in their communities.

Data availability statement

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

Ethics statement

The study was reviewed by the Johns Hopkins Bloomberg School of Public Health (JHSPH) Institutional Review Board (IRB). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements, however oral consent was taken.

Author contributions

BD, RS, and ASh conceptualized and designed the project. BD, YQ, and BT designed data collection tools and facilitated interviews. BD, ASu, and PB analyzed and interpreted the study data. PB, RS, and BD drafted the initial manuscript. RS, ASu, ASh, and SC provided critical review of the manuscript.

All authors reviewed the manuscript and approved the final manuscript as submitted.

Conflict of interest

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

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Impact of educational interventions on the prevention of influenza: A systematic review

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Introduction: Seasonal influenza, a contagious viral disease affecting the upper respiratory tract, circulates annually, causing considerable morbidity and mortality. The present study investigates the effectiveness of educational interventions to prevent influenza.

Methods: We searched PubMed/Medline, Embase, and Cochrane Controlled Register of Trials (CENTRAL) for relevant clinical studies up to March 1 2022. The following terms were used: "influenza," "flu," "respiratory infection," "prevent," "intervention," and "education."

Results: Out of 255 studies, 21 articles satisfied the inclusion criteria and were included in our study: 13 parallel randomized controlled trials (RCT) studies, two cross-over RCT studies, two cohort studies, and four quasi-experimental studies. A total of approximately 12,500 adults (18 years old or above) and 11,000 children were evaluated. Educational sessions and reminders were the most common interventions. The measured outcomes were vaccination rates, the incidence of respiratory tract infection (RTI), and preventive behaviors among participants. Eighteen out of 21 articles showed a significant association between educational interventions and the outcomes.

Conclusions: The included studies in the current systematic review reported the efficacy of health promotion educational interventions in improving knowledge about influenza, influenza prevention behaviors, vaccination rates, and decreased RTI incidence regardless of the type of intervention and the age of cases.

KEYWORDS

influenza, education, prevention, vaccination, systematic (literature) review

Introduction

Health literacy is a flourishing research and practice field concerned with people's capacities to meet the complex demands of health across the course of life in our modern society, which also considers how people find, comprehend, evaluate, use, and communicate health information (1). Health literacy bears great significance in improving the prevention and control of infectious diseases. Therefore, improving

the health literacy of society on infectious diseases could serve as an essential factor in controlling outbreaks and epidemics of infectious diseases worldwide (2). Health education can improve people's knowledge of contagious diseases and consequently promotes the development of appropriate preventive behaviors toward contagious disease. Health education facilitates health promotion and effectively slows down the spread of infectious diseases (2, 3).

Seasonal influenza, an infectious viral disease affecting the upper respiratory tract, circulates annually, causing considerable morbidity and mortality, mainly among adults aged $\geq$ 65 years and children aged $<$ 5 years. Every year $\sim$3 to 5 million cases of severe illness and about 290,000–650,000 respiratory deaths worldwide due to influenza infection are reported (4). The majority of influenza-related mortality (accounting for over 85% of deaths) occurs in adults older than 65 years (5); it is also associated with about 610,000–1,237,000 respiratory hospitalizations among children younger than 5 years worldwide annually (6).

Some randomized controlled trials (RCTs) have been undertaken to determine the efficacy of the educational intervention on influenza prevention (defining its impact on respiratory tract infection incidence, vaccination rate, and improvement of knowledge or preventive behaviors as the primary outcome). However, the results have been inconsistent (3, 7–10). Furthermore, there has been no systematic review investigation educational intervention on influenza prevention to the best of our knowledge. Therefore, this systematic review aimed to assess the studies reporting on the effect of education on influenza prevention.

Methods

This review conforms to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement (11).

Search strategy

The English medical literature search was carried out in PubMed/Medline, EMBASE, and the Cochrane Controlled Register of Trials (CENTRAL) up to February 1 2022.

We used the following MeSH terms: "'Influenza, Human,' 'Influenza B virus,' 'Influenza A virus,' 'education'." Keyword searches were done with combinations of the terms: "influenza," "flu," "respiratory infection," "prevent," "early intervention," "education," "educate," "school," "school-based" and "inform" (See Appendix). Lists of references of selected articles and relevant review articles were hand-searched to identify further studies.

Study selection

The records found through database searching were merged, and the duplicates were removed using EndNote X7 (Thomson Reuters, Toronto, ON, Canada). Two reviewers independently screened the records by title/abstract and full text to exclude those unrelated to the study topic. Clinical studies investigating the relationship between education and influenza were selected. We included RCTs, cohort studies, and case-control studies conducted on healthy individuals who had the capability to understand educational interventions.

Educational interventions can consist of informative contents such as informational e-mails, messages, reminders, virtual or in person educational sessions about hand and respiratory hygiene related to influenza and any means to inform participants about influenza.

The primary outcome assessed was the occurrence of respiratory tract infection (RTI) episodes, vaccination rates, or improvement of knowledge and preventive behaviors among participants. The exclusion criteria were: conference abstract, case report, and reviews.

Other exclusion criteria were receiving any education related to influenza, hand and respiratory hygiene by control group.

Quality assessment

Two reviewers Bardia Danaei and Niloofar Deravi assessed the quality of the studies independently using two different assessment tools; The Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane tool for experimental studies (12, 13).

Third reviewer Mohammad Javad Nasiri was planned to decide if the two reviews couldn't able to agree on a certain point of bias assessment.

The NOS scale evaluates the risk of bias of prospective studies with three domains: (1) selection of participants, (2) comparability, and (3) outcomes. A study can be awarded a maximum of one point for each numbered item within the selection, and outcome categories and a maximum of two points can be given for comparability. Scores of 0–3, 4–6, and 7–9 were assigned for the low, moderate, and high quality of studies, respectively.

The Cochrane tool is based on; use of random sequence generation; concealment of allocation to conditions; blinding of participant and personnel; blinding of outcome assessors; completeness of outcome data and other; selective reporting and other biases. Each study was rated as low risk of bias when there was no concern regarding bias; as high risk of bias when there was concern regarding bias; or unclear risk of bias if the information was absent.

Data extraction

Two reviewers designed a data extraction form and extracted data from all eligible studies, resolving differences by consensus. The following data were extracted: first author, country of origin, type of study, inclusion period, the definition of case and control, age group and sex of cases and controls, and the total number of controls and cases, type of intervention, and outcomes.

Extracted outcomes were categorized into three groups: (1) RTI incidence reported by studies and diagnosed with clinical features or laboratory tests such as RT-PCR, (2) Vaccination rate and uptake among participants, (3) Improvement of knowledge toward influenza or influenza prevention behaviors which were reported as compliance based on charting documentation, questionnaires and surveys.

Results

Twenty-one articles were included via the selection process, which is shown in Figure 1. The studies were classified into 13 parallel RCT studies, two cross-over RCT studies, two case-control studies, and four quasi-experimental studies. Ten of these studies were conducted in the USA, two in Hong Kong, two in Iran, and others in England, Bangladesh, Greece, Australia, South Korea, China and Colombia. The population of these articles consists of approximately 12,500 adults (18 years old or above that) and 11,000 children. The outcome assessment was different between articles. Although the educational interventions were highly variable and often multimodal, all but three studies (8, 14, 15) addressed and emphasized that educational interventions are successful in influenza prevention in terms of respiratory tract infection incidence (16–22), vaccination rate (7, 9, 23–25), and improvement of knowledge or preventive behaviors (9, 26–30) (Tables 1–3).

The setting of these studies varied from the household setting ($n = 4$) (14, 16, 23, 27), over the hospital and healthcare facilities ($n = 7$) (7, 9, 10, 24–26, 28), schools ($n = 6$) (15, 17, 18, 29–31), and University setting ($n = 2$) (20, 22), to the corporation worksites ($n = 2$) (8, 21) and one study was performed on Hajj pilgrims (19).

All 21 studies implemented at least one intervention of a promotional program with educational sessions or informative content and reminders. The educational sessions were characterized by education of the target group through either verbally communicated hand and respiratory hygiene lessons (e.g., instructions by telephone, on the internet, or face-to-face), with training or instructions on how and how frequent to practice hand hygiene and to use face masks or in combination with written or visual media (e.g., information leaflets, posters, video/live demonstration) (7, 9, 15, 17–20, 31). In addition to that, some studies consisted of the provision of hand hygiene materials, either soap (14, 19), alcohol-based hand

sanitizers (14, 15, 18–20, 31), face masks (14, 19, 20), provided by the researchers to every participating individual (14, 19, 20) or to be shared within their cluster or with others in case of provision at a common place (e.g., common courtyards or school toilets) (15, 18, 31).

Quality of included studies

Based on the Newcastle-Ottawa Scale, which was used to evaluate the quality of the observational studies, the mean (standard deviation [SD]) NOS score was 8.0, which is suggestive for a high methodological quality and a low risk of bias of the included studies. More detailed information about the quality assessment of the observational studies can be seen in Table 4.

Risk of bias assessment of the experimental studies according to the Cochrane tool is presented in Table 5. Only four studies (9, 17, 28, 30) have a high risk of bias in the cases of allocation concealment, blinding of participants, and blinding of outcome (Table 5).

Association of educational intervention on RTI incidence

In a study conducted by Little et al., access to a weekly automated web-based intervention for 4 weeks resulted in fewer respiratory infections in the intervention group in 4 months follow up ($P < 0.0001$) (16). In another study, hand and respiratory education with hand sanitizers supplementation in a school for 4 weeks resulted in lower RTI incidence in the intervention group ($P < 0.01$) (18). In the study conducted by Cowling et al. (14) an intervention group received hand and respiratory hygiene education, and another intervention group received education plus face masks. The control group received only lifestyle education. In 36 weeks, follow-up, there were significant differences between RT-PCR confirmed influenza cases ($P = 0.04$), but after that, the difference became non-significant ($P = 0.283$) (14). In another study conducted on Iranian hajj pilgrims in 2012, educational intervention with personal hygiene packages including alcohol-based hand rubs, surgical face masks, soap, and paper handkerchiefs resulted in significantly less Influenza-like illness (ILI) in the intervention group ($P < 0.001$). In this study, ILI was defined as at least two of the following during their stay: fever, cough, and sore throat (19). Aiello et al. (20) study included young adults from university residence halls during the 2006–2007 influenza seasons. The intervention group received respiratory hygiene education with face masks and hand hygiene equipment, resulting in significantly reduced ILI compared to the control group ($P < 0.05$) (20). Stedman-Smith et al. prepared a 4-min online training video and three brief monthly surveys as the intervention, which caused a statistically significant relative

FIGURE 1
Flow chart of the number of studies identified and selected into the systematic review and meta-analysis.
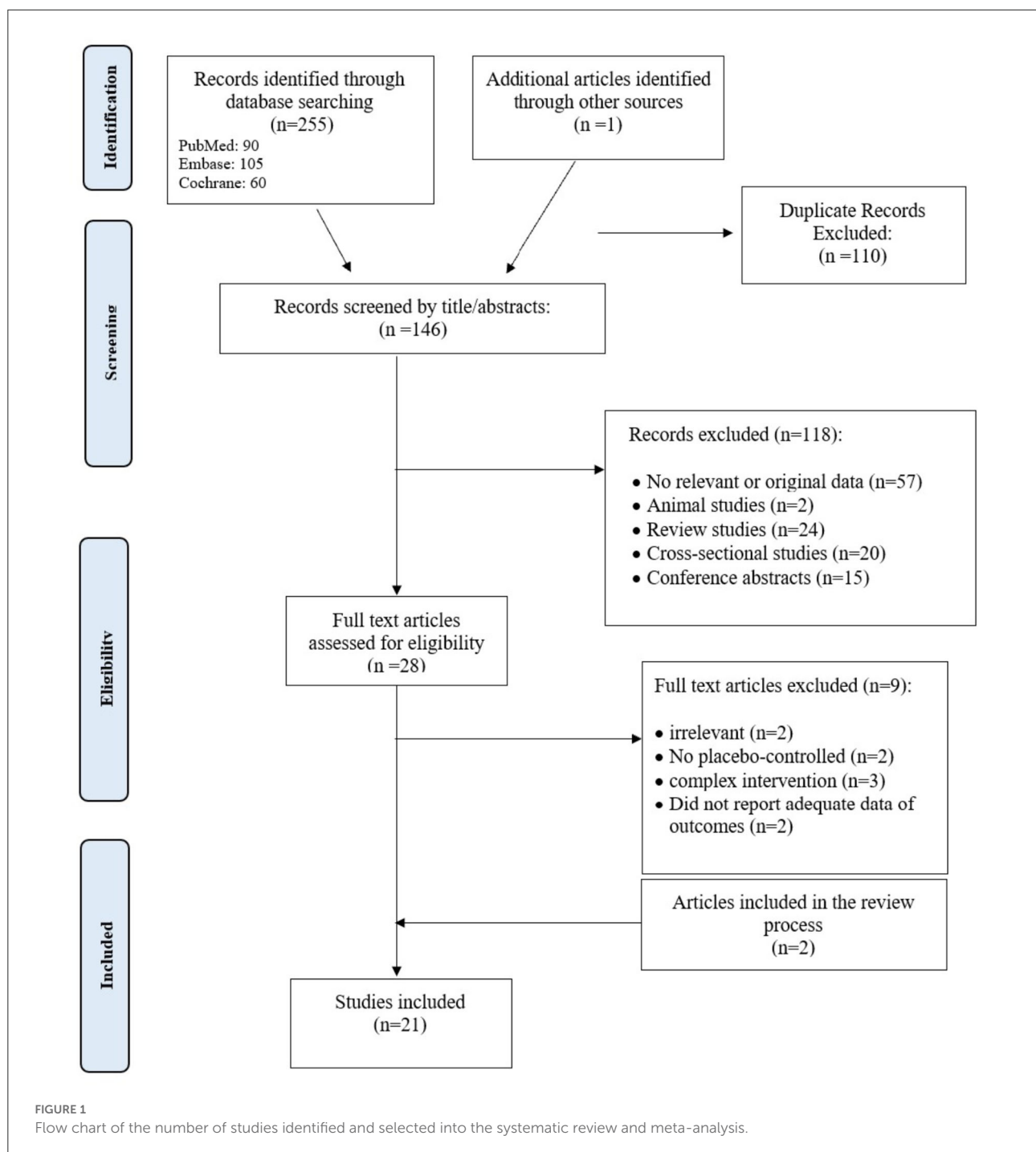
reduction of 31% in acute respiratory infections and influenza-like illnesses ($P = 0.037$) (21). In the White et al. study, participants in the experimental halls were exposed to a health campaign designed to increase awareness of the importance of hand hygiene in avoiding the flu. The intervention and control groups were both supplied with hand sanitizers. After 8 weeks of follow-up, the experimental group reported 26% fewer ILI

than the control group ($P < 0.0001$) (22). Correa et al. (31) conducted a parallel RCT study on school children in which the researchers provided alcohol-based hand rubs and training on proper use for intervention group with 30-minute monthly sessions for 9 months. They reported significant reductions in risk for acute respiratory infections in the second and third trimester ($P < 0.05$, $P < 0.001$, respectively) (31). In another

TABLE 1 The association of educational interventions on RTI incidence.

Author	Year	Country	Type of study	Participants' age category	Educational intervention type	Association of educational intervention on RTI incidence reduction
Little et al. (16)	2015	England	Parallel RCT	Adult	Reminders and informative content	Yes
Biswas et al. (18)	2015	Bangladesh	Parallel RCT	Children	Educational sessions about hand and respiratory hygiene	Yes
Cowling et al. (14)	2009	Hong Kong	Parallel RCT	Both	Educational sessions about hand and respiratory hygiene	No*
Aelami et al. (19)	2015	Iran	Parallel RCT	Adult	Educational sessions about hand and respiratory hygiene	Yes
Aiello et al. (20)	2010	USA	Parallel RCT	Adult	Educational sessions about hand and respiratory hygiene	Yes
Stedman-Smith et al. (21)	2015	USA	Parallel RCT	Adult	Educational sessions about hand and respiratory hygiene	Yes
White et al. (22)	2014	USA	Parallel RCT	Adult	Educational sessions about hand and respiratory hygiene	Yes
Correa et al. (31)	2008	Colombia	Parallel RCT	Children	Educational sessions about hand hygiene	Yes
Stebbins et al. (15)	2008	USA	Parallel RCT	Children	Educational sessions about hand and respiratory hygiene	No#
Or et al. (17)	2019	Hong Kong	Quasi-experimental	Both	Educational sessions and informative content	Yes

*In short period of time (<=36days) it has been proven to be effective (P = 0.04) but in longer period it does not have a significant association (p = 0.22).
#They found no significant effect of the intervention on the outcome of all laboratory confirmed influenza (influenza A and B) cases but laboratory-confirmed influenza A infection rate in intervention schools was significantly lower.

parallel RCT study conducted by Stebbins et al. (15) on students of 10 elementary schools, the researchers implemented an educational program called "WHACK the Flu" in intervention schools in addition to providing alcohol-based hand sanitizers. The researchers used RT-PCR to confirm influenza cases. They found no significant effect of the intervention on the outcome of all laboratory confirmed influenza (influenza A and B) cases but they reported significant fewer laboratory-confirmed influenza A infection in intervention schools. In Or et al. (17) quasi-experimental study training program for kindergarteners and their parents led to fewer flu-like signs and symptoms after the intervention ($P = 0.005$).

Association of educational intervention on vaccination rate

In the study conducted by Kempe et al. (24) one to three reminders were sent to the parents of children in Colorado and New York primary care practices. The main outcome was documentation of ≥1 influenza vaccine within 6 months. There was no significant difference in Colorado in the one reminder and three reminders intervention group, but there was a significant increase in vaccination rates in all other intervention groups. In the Szilagyi study, patients due for an influenza vaccine in the intervention group were sent a letter reminding them about the importance of influenza vaccination, its safety, and morbidity associated with influenza. There was a statistically significant increase in vaccination rates among the intervention group ($P = 0.008$) (25). In another study, healthcare Workers participated in surveys and were educated about vaccination, and the result of intervention was evaluated by comparing the vaccination rates of the year of the intervention with the rates of the 2 years before and the year after. The intervention led to an increase in seasonal influenza vaccine uptake by the healthcare workers ($P < 0.001$) (7). In another study conducted by Schensul et al., there was a significant increase in vaccination rates among participants in a twice-a-week informative meeting held for 2 months ($P = 0.01$) (23). In the Ferguson et al. study, a 5-min

TABLE 2 The association of educational interventions on vaccination rate.

Author	Year	Country	Type of study	Participants' age category	Educational intervention type	Association of educational intervention on vaccination rate
Kempe et al. (24)	2015	England	parallel RCT	Adult	One reminder and informative content	Yes
Kempe et al. (24)	2015	England	parallel RCT	Adult	Two reminders and informative content	Yes
Kempe et al. (24)	2015	England	parallel RCT	Adult	Three reminders and informative content	Yes
Szilagyi et al. (25)	2019	USA	Parallel RCT	Both	One reminder and informative content	Yes
Szilagyi et al. (25)	2019	USA	Parallel RCT	Both	Two reminders and informative content	Yes
Szilagyi et al. (25)	2019	USA	Parallel RCT	Both	Three reminders and informative content	Yes
Kopsidas et al. (7)	2020	Greece	Parallel RCT	Adult	Educational sessions and informative content	Yes
Schensul et al. (23)	2009	USA	Parallel RCT	Adult	Educational sessions with ongoing financial and vaccination support	Yes
Ferguson et al. (9)	2010	Australia	Cross over RCT	Both	Educational sessions and informative content	Yes
Bourgeois et al. (8)	2008	USA	Parallel RCT	Adult	Informative content	No

education session was developed to inform patients/caretakers about the risk of respiratory viral infection, preventive measures, and efficacy. The primary outcome was awareness of and attitudes toward preventive strategies, and the vaccination rate significantly increased in the intervention group ($P < 0.0001$) (9). In the study conducted by Bourgeois et al., participants were recruited from eight Hewlett Packard Corporation work sites in the northeastern United States in the fall of 2005. They evaluated an electronic system to modify knowledge, beliefs, and behavior around influenza. They sent weekly messages for 4 weeks to the intervention group, but there was no significant difference in the immunization rate between the intervention and control groups ($P = 0.5$) (8).

The association of educational interventions on the improvement of knowledge or preventive behaviors

In the study conducted by May et al. the investigators sent an informational e-mail to healthcare providers *via* an electronic medical record system, explaining the importance and proper use of infection control precautions for patients with clinically suspected or confirmed influenza. The email was repeated every month for 7 months for the intervention group. After this intervention, the overall compliance with transmission precautions increased ($P = 0.015$) (26). As mentioned above, Ferguson et al. provided a 5-min education session to participants in the intervention group to increase their awareness and attitude toward preventive measures which evaluated by self-administered questionnaires ($P < 0.0001$) (9). Bourgeois et al. sent weekly messages to participants in the intervention group to modify knowledge, beliefs, and behavior around influenza for 4 weeks which could not improve their knowledge and preventive behaviors significantly compared to the control group ($P = 0.5$). Surveys containing questions on influenza knowledge, beliefs, and behavior was used to collect data. (8). In the study conducted by Koep et al. (29) teachers and students were recruited to participate in 4 to 6 weeks of the internship, including education about vaccine design and effect, hand hygiene and cough etiquette, germ growth, and immune system functioning. Talking drawings (TD's) strategy were used to assess pre/ post intervention changes in students understanding and emerging student language. The results showed improvement in influenza prevention understanding ($P < 0.0006$) (29). In another quasi-experimental study conducted

TABLE 3 The association of educational interventions on the improvement of knowledge or preventive behaviors.

Author	Year	Country	Type of study	Participants' age category	Educational intervention type	Association of educational intervention on knowledge and preventive behaviors
May et al. (26)	2010	USA	Case-control	Adult	Educational sessions and informative content	Yes
Ferguson et al. (9)	2010	Australia	Cross over RCT	Both	Educational sessions and informative content	Yes
Bourgeois et al. (8)	2008	USA	Parallel RCT	Adult	Informative content	No
Koep et al. (29)	2013	USA	Case-control	Children	Educational sessions and informative content	Yes
Kim et al. (27)	2020	South Korea	Quasi-experimental	Adult	Educational sessions and informative content	Yes
Sadeghi et al. (28)	2017	Iran	Quasi-experimental	Adult	Educational sessions and informative content	Yes
Wangvv et al. (30)	2016	China	Quasi-experimental	Children	Educational sessions and informative content	Yes

TABLE 4 Quality assessment of the observational studies included in the meta-analysis (The NOS tool).

Author	Selection			Comparability			Outcome			Total quality score
	Representativeness of Exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjust for the most important risk factors	Adjust for other risk factors	Assessment of outcome	Follow-up length	Loss to follow-up rate	
Koep et al. (29)	1	1	1	1	1	0	1	1	1	8
May et al. (26)	1	1	1	1	1	0	1	1	1	8

by Kim et al. on rural elderly individuals, a health education program aimed at preventing respiratory infections with 4 weekly sessions and a reinforcement session one to 6 months after the initial training led to a significant increase in respiratory infection prevention practices ($P < 0.001$). In this study the respiratory infection prevention knowledge scale developed by Kwon and Yu were used for measurement of knowledge (27, 32). In a quasi-experimental study conducted by Sadeghi et al. (28) in Iran on pregnant women, informative content including the definition of flu, its symptoms, transmission, prevention, diagnosis, and treatment was educated within 2 weeks to the intervention group, which caused significant

improvement in knowledge and preventive behaviors ($P = 0.001$). Health Belief Model Questionnaire was used in this study (28). In another quasi-experimental study, Wang et al. designed an education program for children, including playing promotion cartoons, developing lectures, giving out handbook copies, and making hand copy and blackboard newspapers, which held monthly for one year and led to significant improvement of behavior toward respiratory infectious disease (RID) in the intervention group ($P < 0.05$). Authors used a self-designed questionnaire including items concerning knowledge on RID and RID prevention behavior for in this study (30).

TABLE 5 Quality assessment of the experimental studies included in the meta-analysis (the Cochrane tool).

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Little et al. (16)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Biswas et al. (18)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Cowling et al. (14)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Aelami et al. (19)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Aiello et al. (20)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Stedman-Smith et al. (21)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
White et al. (22)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Or et al. (17)	High risk	Low risk	High risk	Low risk	Low risk	High risk	Low risk
Kempe et al. (24)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Szilagyi et al. (25)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kopsidas et al. (7)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Schensul et al. (23)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ferguson et al. (9)	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Bourgeois et al. (8)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kim et al. (27)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sadegh et al. (28)	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wang et al. (30)	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Correa et al. (31)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Stebbins et al. (15)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk

Discussion

The present study found that educational interventions show efficacy for influenza prevention by impacting respiratory tract infection incidence, vaccination rate, and improvement of knowledge or preventive behaviors. Several explanations were reported, which are summarized in the following.

A study in Greece aimed to increase healthcare workers' uptake of seasonal influenza vaccination in a tertiary-care pediatric hospital with a low-cost, tailor-made, multifaceted strategy. This strategy increased the vaccination rate by overcoming barriers such as concerns about the safety and effectiveness of the vaccine, the belief that one does not belong to a high-risk group, logistical concerns, and concerns about side effects of the vaccine (7). Another study in the United States aimed to increase residents' ability to make informed decisions about vaccination and build internal and external infrastructure to support sustainability over time. Evaluation results showed that the educational intervention achieved most of its desired goals at all levels. It achieved significantly increased pro-vaccination knowledge, beliefs, and norms with increased correct social thoughts toward vaccination. It reduced vaccination fears among peer

implementers and participating residents and finally improved the vaccination rate in the intervention building (23).

A South Korean study reported highly positive outcomes of an educational program for respiratory infection prevention among rural elderly residents (27). The reasons for the program's high efficacy were that it was developed based on the processes of observational learning (i.e., attention, memory, retention, and motivation). Key concepts from this theory, such as imitation, cognition, reinforcement, and self-efficacy, were also applied to the development of the program. One of the four observational learning processes, attention, was incorporated in the program in such a way as to enhance trainees' interests and motivation: the trainees were asked to think about why the topic of each training session was necessary. They were also asked to reflect on what they had learned by singing a song or taking a pledge of practice. The memory process, which involves the cognitive storage of information learned from observation, was promoted in the program through video materials used to stimulate both vision and hearing among the trainees. To enhance their concentration, various instruments were used, such as a dental model, a view box, masks, and a walking mat. These instruments helped to demonstrate actions like correct hand washing, correct walking, etc. Next, the retention process,

which involves determining the consistency between what one learns and how one subsequently behaves through internal feedback, was invoked among trainees through self-observation and self-correction, i.e., the trainees were guided to adapt theirs to the model's behavior. As the final step, the motivation process was stimulated by encouraging trainees to engage in program practices. The trainees sang a song that included keywords and key concepts from each training session. In addition, the trainees were also asked to take a pledge of practice to review what they had learned (27).

Rewards were used to increase participation among the trainees across all sessions. At the beginning of each session, rewards were given to the trainees who shared what they had learned from the previous session with their peers. Some trainees were also rewarded with items for respiratory infection prevention such as a handkerchief, hand sanitizer, and toothbrush/toothpaste for completing tasks, memorizing the songs and pledge of practice, or correctly answering questions on the quiz. In the final session, certificates and prizes were awarded to the trainees for participating in the program. For the program, instructors were selected based on whether their ages approximated the trainees' age to enhance rapport and familiarity (27). Such an approach has previously been applied to increase compliance with respiratory infection prevention practices (33).

A Chinese study reported the efficacy of health education on the knowledge and behavior of students toward RID. According to this study, in primary, middle, and high schools in China, students are busy with various exams and lack awareness and enthusiasm for learning about RID. At the same time, Chinese schools often neglect to teach infectious disease-related courses, leading to a lack of health education toward RID among school students and hindering the improvement of the accuracy rate and scores of RID of these students. Such a phenomenon may be one of the leading causes of the outbreak and epidemic of RID in primary, middle, and high school campuses (30). Therefore, educational interventions could lead to positive outcomes in this group. An Australian study aiming to measure and increase patient/household awareness of RV infection and preventive measures suggested that patients preparing for hematopoietic stem cell transplant (SCT), and their families and friends, understood that RVs pose a risk to patients after transplantation. Still, they underestimated its severity and lacked knowledge on effective prevention methods. A brief information session nested in a broader educational forum increased knowledge and acceptability of prevention methods, particularly family influenza vaccination, with an associated increase in household vaccination evident at the time of hematopoietic SCT admission (9).

Although in another study in the United States, the intervention did not have a statistically significant effect on the knowledge elements assessed (probably due to small sample size); however, it did have a considerable effect on certain beliefs surrounding influenza. At the end of the study, participants in the intervention group were more likely to believe that the influenza vaccine was effective, that there were actions they could take to prevent the flu, and that the influenza vaccine was unlikely to cause a severe reaction (8).

To conclude, according to the results of included studies, educational interventions could be effective in preventing Influenza. We recommend using validated educational tools clearly described, widely generalizable, and easily reproducible. We also encourage cluster randomized trials to investigate the efficiency of both organizational and educational interventions and incorporate a cost assessment into the study design. In the case of non-RCTs, addressing the threats to internal validity is required (e.g., by using a parallel control group and a time-series method with multiple observations conducted both before and after interventions). Statistical analyses are encouraged to include assessments of secular trends rather than comparisons of mean values before and after educational interventions. The sample in most studies was mixed gender cohorts. Hence, to ascertain whether between-gender differences exist, future studies must include sub-analysis by gender. Notably, the lack of a detailed description of the educational strategies content, including an assessment of validation of the educational interventions, needs to be addressed. Baseline characteristics such as the learner's academic level or job may also affect the ideal type of intervention for the participants. Future studies should also address whether reminders are needed and at what intervals they should be repeated.

There are some limitations in the current systematic review. Some studies used education methods that were not easy to use by all the population. For example, older adults were less likely to use modern educational methods. Other limitations of the studies were the limited number of participants and institutions and the duration of studies. The studies also had different settings and methodologies. Likewise, due to the limited number of studies, potential factors that lead to overall heterogeneity were not examined.

In conclusion, the findings of our systematic review suggest that health promotion educational interventions, i.e., regardless of the type of intervention and the age of cases, can improve knowledge and preventive behaviors vaccination rates and decrease RTI incidence.

Data availability statement

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

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.978456/full#supplementary-material

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Status quo and problem analysis of cervical cancer screening program in China: Based on RE-AIM framework

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Background: An organized cervical cancer screening program is an effective method to prevent and control cervical cancer. This study aims to find barriers and facilitators in the implementation process of National Cervical Cancer Screening Program in Rural Areas (NACCSPRA) in China through program evaluation, and thus propose suggestions for optimization of the program.

Methods: Through stratified sampling, 8 provinces (autonomous cities/districts) in eastern, southern, western, northern, and central China were selected for evaluation of NACCSPRA based on the RE-AIM framework. We obtained 15 program providers' experience and perspectives through semi-structured interviews. The data was analyzed using a combination of deductive and inductive analysis methods.

Results: The study found that NACCSPRA mainly serves women with rural household registration or urban minimum living guarantee. Population mobility and certain demographic characteristics such as low education and poor health awareness are common participation barriers, while program publicity acts as a facilitator. A screening program's direct benefit is to promote early detection and treatment of cervical cancer, and its perceived indirect effect is to raise people's health awareness. The proportion of regions adopting the project is relatively high, and factors affecting employees' participation are screening workload, working environment, welfare benefits, degree of preference for grassroots work, and whether the project is included in the performance appraisal; In terms of implementation, there are disparities in screening methods, network informatization levels, and capital investment in various regions. Poor development of screening information system and insufficient screening funds are significant barriers to improvement of project implementation. In contrast, the overall implementation of follow-up is better; related policies issued by the local government and financial subsidies for poor women ensure the maintenance of the project.

Conclusion: Shortage of funds is an important problem faced by current screening project, which negatively influences upgrade of cervical cancer prevention strategy, implementors' working environment, and impedes

improvement of information network. In addition, defects in population coverage, especially in mobile population also deserves attention. The study found barriers and facilitators of NACCSPRA perceived by project providers and provided a theoretical foundation for project optimization.

Introduction

Cervical cancer is the fourth most common cancer and cause of death among women worldwide. In 2020, 6,04,127 newly diagnosed cases and 3,41,831 death cases were reported worldwide (1). Significant regional differences in cervical cancer morbidity and mortality, which are associated with regional economic development, medical resource allocation, and the implementation of cervical cancer prevention and control projects, should not be neglected. In high-income countries, due to widespread vaccination, effective implementation of screening programs, improvement of cancer detection and treatment technologies, morbidity, and mortality of cervical cancer have dropped significantly. However, incidence still tends to increase in Eastern Europe and parts of sub-Saharan Africa (2). In 2020 WHO issued the global strategy to accelerate the elimination of cervical cancer through tertiary prevention, putting forward the target of reaching the goal of 90-70-90 by 2030.

Age-standardized incidence and mortality of cervical cancer in China in 2020 were 10.2 and 5.3 per 1,00,000 respectively, which shows that cervical cancer is still an important cause of disease burden (3). HPV vaccination and routine cervical cancer screening have proven to be effective in preventing cervical cancer (4). However, coverage of HPV vaccination is low in China because of the high price and limited supply of HPV vaccine. As a result, cervical cancer screening is now the primary method of prevention in China. In 2009, China launched the National Cervical Cancer Screening Program in Rural Areas (NACCSPRA) targeted at women aged 35–64 with rural household registration or who reached the standard of urban minimum living guarantee, series of testing including HPV testing (only conducted in HPV pilot areas), cervical cytology testing, colposcopy examination, and histopathological examination are conducted, only women with abnormal testing result receive next-level examination, and then final follow-up or treatment regimens are designed based on testing results. Nearly120 million free cervical cancer screenings have been carried out up to 2019 and the coverage rate of cervical cancer screening in China has increased to 21.4%, but it is still significantly lower than that in high-income countries and regions, such as Sweden (82%) (5) and America (81.6%) (6). Furthermore, prediction models have revealed that, under

current prevention strategies in China, the incidence of cervical cancer still has the tendency to rise (7). This suggests that China's screening strategies and project implementation remain problematic and need to be improved.

The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework was proposed by Russell E. Glasgow et al. It contains reach (R), effectiveness (E), and maintenance (M) dimensions at the individual level, as well as adoption (A), implementation (I), and maintenance (M) dimensions at staff and setting level, and definitions of each dimension are clarified in Glasgow's commentary (8). Since its inception, the model has been widely used in the systematic evaluation and planning of clinical research (8) as well as local and national health projects (9), including the evaluation of intervention effects on obesity, diabetes, and other diseases (10), as well as the effects of some health education projects for medical staff or patients (11).

RE-AIM framework has also been used in the field of cervical cancer screening. A study in Argentina used the framework to compare the effectiveness of programmatic HPV testing and cytology-based screening, verifying the feasibility of effective HPV testing programs in the real world in middle-income countries (12, 13). Mizota et al. applied RE-AIM framework to evaluate effectiveness of invitation materials using social marketing and behavioral economics approaches for improving screening rate of several cancers (14). The RE-AIM framework is systematic and comprehensive, focusing more on translating theoretical research into practical application than traditional evaluation theories. Therefore, evaluating a project from various components and dimensions, balancing internal and external effectiveness, and paying attention to contextualized problems during the dissemination and implementation process (9). Currently, researches on cervical cancer screening in China mainly emphasize the comparison of different screening strategies using certain health outcomes such as screening coverage, the detection rate of precancerous lesions, and the incidence and mortality of cervical cancer (7, 15, 16), while ignoring the impact of other factors related to implementation process, such as intervention environment, implementors' complement and attitude toward the project, the impact of the policy environment, etc. The RE-AIM framework was selected for this study to address the issue of limited evaluation indicators in previous studies, identify potential roadblocks

to the transition of theoretical screening strategies to feasible programs in a real-world setting, and thus promote the optimization of current and future screening programs.

Early detection of cervical cancer plays a vital role in better treatment and prognosis of the disease. Due to the large population in China, the incidence number of cervical cancer accounts for nearly one-fifth of the total incidence number worldwide. Therefore, the effective implementation of cervical cancer screening in China is of great significance in reducing the incidence and mortality rate of cervical cancer worldwide. Our study selected the RE-AIM framework to evaluate the implementation of NACCSPRA in China, to discover barriers and facilitators through the experience and perceptions of project providers, and thus, provide a theoretical basis for optimization of organization and implementation of screening programs in the future.

Method

Participants and setting

First of all, we divided China's provinces, autonomous regions, and municipalities into five large areas according to geographical location: eastern, southern, western, northern, and central part. For the cervical cancer screening project evaluation, 1–3 provinces in each region were selected using stratified random sampling. The population distribution determined the number of regions selected in each area. Finally, Shanghai, Zhejiang Province, Jiangsu Province in the eastern region; Yunnan Province in the southern region; Ningxia Hui Autonomous Region in the western region; Liaoning Province in the northern area and Anhui Province, Hunan Province in the central region, totally 8 provinces (autonomous cities/districts) are selected.

Then we contacted providers of NACCSPRA in those selected regions for interviews. Inclusion criteria for respondents are participation in on-site cervical cancer screening or organization and management of local NACCSPRA over the past year. Finally, 3 staff in Provincial Maternity and Child Health Centers, 7 staff in the municipal and county-level Maternity and Child Health Centers, 5 medical staff of cooperative medical institutions, and a total of 15 persons were selected to be interviewed. All members participated voluntarily and anonymously.

Data collection

Under the guidance of the RE-AIM framework, we have collected qualitative data about the implementation condition of NACCSPRA in different regions. The qualitative data sources include interviews with program providers and analysis of screening documents and data.

A semi-structured interview guide was developed based on the RE-AIM framework (17), previous evaluation research (12, 13), and expert recommendations (Table 1). We collected background information, implemented pilot surveys and revised interview outline according to experts' suggestion before formal interview. From August 2020 to May 2021, face-to-face or online interviews with 15 participants were conducted by 5 researchers, guided by the self-designed interview outline. All researchers had interview experience before and received relevant training. Each interview lasted about 40–60 min, the content of which was recorded by audio recording, and then transcribed verbatim and verified by independent transcribers to ensure that the research findings were based on the interviewee's statement rather than the researcher's existing knowledge or experience. Audio materials were destroyed after transcription to protect the participants' privacy.

At the same time, we asked participants to provide relevant documents (policy documents, implementation scheme, etc.) and available data about participation of local cervical cancer screening projects if possible. Researchers sorted out valid information in those documents based on the RE-AIM framework as supplements to interview data and compared requirements in those documents with the actual implementation situation reflected by the interviewers.

Data analysis

Within 24 h after the interview, the audio recordings were transcribed verbatim by an independent transcriber and saved in Microsoft Word documents separately. The researcher perused and be familiar with the content of the interviews. The data was then analyzed using a combination of methods, the first of which was iterative deductive content analysis. We take the RE-AIM framework as the initial coding structure, coding related contents by pre-designed codes according to 5 dimensions of the RE-AIM framework. Second, inductive content analysis was used to identify emerging codes and concepts that did not match the pre-designed codes, then sorting all codes into 5 dimensions of the RE-AIM framework and charting data into the framework matrix. During the data analysis process, research members hold a formal meeting every 2 weeks to discuss emerging codes in each dimension of the RE-AIM framework, their categorization, and interpretation, focusing on issues or disagreements generated to reach consensus.

Result

Reach

Reach, the criteria of degree of individual participation aim to study the population participation, representativeness

TABLE 1 Interview guideline and key findings based on RE-AIM framework.

RE-AIM elements	Descriptions	Findings
Reach	• Who's the target population, and how about their participation situation? • What factors contribute to the participation/non-participation of the participants? • What might have been done to attract more of the target population to participate?	• Target population: women aged 35-64 with rural household registration or reached the request of urban minimum living guarantee, and most regions expand the scope of screening • The coverage rate of the task volume is higher than 80% • Non-participation of the floating population is severe problem • Propaganda is a facilitating factor for screening participation
Effectiveness	• What's the perceived positive/negative impact of the screening program on participants?	• Promote early diagnosis and treatment of cervical cancer and precancerous lesion, and thus improve patients' prognosis and quality of their lives • Psychological stress and influence on family relationships are potential negative impacts of detection of cervical cancer
Adoption	• What factors contributed to the organization and its individuals taking up the intervention? • What factors affect the participation and enthusiasm of staff members in related organizations?	• The NACCSPRA covered more than 80% of counties (cities, districts) nationwide, and many regions interviewed have expanded coverage areas in recent years. • Collaboration level between medical institutions reflected in different regions varies a lot. • There are differences in working enthusiasm of the staff, which are influenced by factors such as workload, working environment, employee benefits, and whether screening work is included in performance appraisal.
Implementation	• How was the screening program implemented? What influenced the implementation of each part of the program? • How about the cost and budget of the program?	• Screening methods among different regions vary from Pap test and TCT to combined screening (HPV + cytological test). • The construction of information systems is inadequate and uneven in different regions, which can be roughly divided into three development stages. • The completion rate of follow-up is required to be higher than 95%, and most patients have high compliance. • The amounts of subsidies varies from place to place, and all regions reported an insufficiency in screening funding.
Maintenance	• What has been made to ensure the maintenance of the program?	• Different regions constantly adjust and improve relevant policies based on national projects and local situations. Some regions have also carried out regional-characteristic screening projects and issued subsidy funds to ensure those with positive screening outcomes receive appropriate follow-up treatment.

of participants and non-participants, and possible influencing factors of the program's accessibility.

Target population

The target population of NACCSPRA is women aged 35–64 with rural household registration or who reached the standard of urban minimum living guarantee. Most regions expand the scope of screening, such as extending the covered age range to 70 years old, taking into women with certain conditions such as retirement, women in public welfare positions, women in single-parent families, etc. Women with urban household registration are also integrated into the target population in some pioneer districts.

All regions reach a coverage rate higher than 80% of the task volume. Those who aren't covered are screened primarily through hospital opportunistic screening and occupational health examinations, with no guarantee of participation.

> "Screening in the outpatient department isn't covered by health insurance, so acceptance depends on one's economic status, individual health awareness, and attention, and those out of coverage range rarely participate in screening initiatively."—Changsha Province

Non-participation has improved in recent years, but it has not completely disappeared. The mobile population is an important characteristic for non-participants, which was mentioned repeatedly by interviewees, as it requires household

registration for a free screening. Among them, screening leakage of inflow population in economically developed areas and outflow population in underdeveloped areas are serious. Other general characteristics of non-participants include older age, lower education level, poor health awareness, and distrust of the medical system. In addition, cognitive biases on screening and the low family status of women will also affect participation, which is more serious in remote areas.

> *"Screening barriers differ in different age groups. Many people under 45 work outside as migrant workers; some of those over 45 years old have a deviation in their understanding of screening, believing that screening is harmful to them or bad things, such as divorce, will happen if diagnosed with the disease."*—Ningxia Province

Publicity of the program

Although respondents believe that propaganda facilitates screening participation, they also believe that common obstacles such as insufficient publicity, a lack of professionalism among personnel, and a lack of standardization in the form, frequency, effectiveness, and funding of publicity still exist. In addition, region-specific barriers should not be ignored, especially in remote regions, such as language barriers and inconvenient transportation.

> *"Due to the complex terrain and scattered villages, residents do not have convenient transportation tools, sometimes even ambulances are used to pick up residents for screening. Another problem is that some people speak minority languages which propaganda staff cannot grasp, leading to communication barriers."*—Yunnan Province

Effectiveness

Our research mainly discusses the effectiveness of the program from the project providers' perspective. We focus on both positive and negative effects perceived by program providers and the reasons behind them.

Program implementers generally believe that the screening program is of great significance to promote screening coverage and early diagnosis and treatment of cervical cancer and thus reduce incidence. Besides the direct benefits, regular publicity can improve people's health awareness, and early detection of cervical lesions has a positive effect on a patient's quality of life. In contrast, the possibility of disease detection causing psychological stress or affecting family relationships is a potential negative impact.

> *"Every year, it is possible to detect 2–3 cancers and 20–30 precancerous lesions. It is reasonable to say that it will reduce the incidence rate and improve people's awareness of the importance of screening."*—Yunnan Province

> *"Patients suffer from psychological stress during early treatment, such as anxiety and fear, but quality of life will be improved after receiving treatment, and corresponding lifestyle changes will be adopted by patients."*—Ningxia Province

Adoption

Adoption refers to the proportion and representativeness of the setting in which a given policy is adopted and the staff who participate in the program.

Covered area

The NACCSPRA covered more than 80% of counties (cities, districts) nationwide from 2009 to 2019. There were 21 provincial administrative regions that covered all rural areas and 13 that covered both urban and rural areas.

In recent years, many places interviewed have expanded screening coverage areas. For example, Ningxia Hui Autonomous Region has expanded from 6 counties (districts) to 22 counties (districts) and the Ningdong region since 2012; Dalian City achieved full coverage of agricultural counties in 2017.

Implementation institution

Screening tasks are assigned to primary screening institutions and receiving institutions. The former is responsible for initial screening and abnormal case management, and the latter should be capable of further diagnosis and treatment for those with abnormal screening results. The level of collaboration between medical institutions reflected varies among different regions. Shanghai, Zhejiang, and Yunnan reported insufficient information exchange among institutions and unclear distribution of responsibilities. In contrast, Ningxia and Anhui Provinces stated that the division of labor is clear with better cooperation.

> *"Local maternal and child health care hospitals led the screening, and Women's Federation arranged staffs to attend classes, but participation level of other institutions was not high"*—Yunnan Province

Women are encouraged to go to primary screening institutions on their own or in groups in most areas. However, due to traffic problems and low screening awareness in Yunnan, screening teams are sent to the countryside for testing.

Nevertheless, this method is limited in application due to time-consuming and laborious.

> *"In some areas, we send screening teams to the countryside, but this method has problems of 10 more people needed, higher expense and poor site conditions"*—Yunnan Province

Attitude of program provider

After training and assessment, most screening staff are hired directly by a related screening agency. Although having a high degree of recognition of the project, heavy workload, noisy working environment, and poor welfare benefits negatively affect staffs' participation enthusiasm. Meanwhile, affection for grassroots work, including screening work into performance appraisal are stimulus factors. However, some reported that performance appraisal is mainly for screening institutions instead of individual physicians.

> *"The screening workload is heavy, and sometimes extra work is inevitable. Each doctor screens more than 60 people every day with low salary, which may lead to complaints."*—Shanghai

Implementation

This dimension focus on intervention agents' fidelity to screening protocol, adaptations made to the original plan, and the cost of the intervention.

Screening method

Pap smears are used in Shanghai Pudong, Yunnan, and part of Anhui Province, TCT is used in Shanghai Fengxian District, Dalian Pulandian District, and Changhai County. Hunan, Ningxia, Zhejiang Province, and some HPV test pilot areas switched to combined methods of HPV and cytology for preliminary screening. Participants with abnormal preliminary screening results will be examined by colposcopy.

According to the findings, on-the-spot monitoring and sample checking are the most common methods of quality control. While regulations about quality control are contained in screening documents, a complete quality control implementation system remains absent.

> *"The screening team will monitor screening quality on-site, and the Maternal and Child Health Center will select test results randomly for quality evaluation."*—Shanghai

> *"There are quality control requirements for sample testing, but conduction of regular spot checks will meet difficulties. Instead, we inspect screening work on-site for quality control."*—Ningxia Province

Information collection and utilization

At present, patients diagnosed with cervical precancerous lesions or cervical cancer will be reported to the Regional Maternal and Child Health Information System and National Cancer Registry. But the development of screening information systems varies from place to place, of which the construction level can be roughly divided into 3 stages: The first stage, no screening information system (Shanghai Pudong District) or the system is still under construction (Ningxia). Participants' data collection is currently limited to on-site registration on paper. The second stage involves the establishment of regional registration systems to digitally input participant information, but the system is only accessible to staff and does not allow patients to interact (Liaoning). In the third stage, the information system is complete and doctor-patient interaction is achievable. Participants can use the system to inquire about their screening results, and online follow-up management is also available. For example, the "Artificial Intelligence Internet + Cloud Platform" in Yunnan Province and the "Healthy People's Livelihood Information System" in Changsha City have achieved remarkable achievements.

The construction of a large-scale and interchangeable information system has several obstacles to be resolved, such as high capital investment, difficulty in system operation, and using barriers for grassroots staff.

> *"The biggest problem is insufficient funds. Although there is financial support from both national and provincial levels, it is very expensive to establish and maintain a relatively extensive information system. On the other hand, various obstacles will appear during the actual use process."*—Ningxia Province

Follow-up

Follow-ups are carried out according to national requirements with corresponding follow-up strategies for different lesion grades, and follow-up rates are required to be higher than 95%. The completion rate increased through effective measures such as door-to-door notification of incompliant people. However, it's difficult to avoid isolated cases going unnoticed or refusing to take action.

> *"Follow-up should last for at least 3 months and must have a final follow-up result. There used to be cases of loss to follow-up (such as changing the phone number), but now such things happen less often."*—Anhui Province

> *"Some participants will not strictly follow the recommended standards to receive a subsequent examination and corresponding supervision is deficient."*—Zhejiang Province

The screening agency will make treatment recommendations for patients with varying degrees of disease severity. However, poor economic conditions, particularly in underdeveloped areas, are deterrents to patients continuing their treatment. In contrast, supports from medical staff and family members both have positive impacts.

> *"Most patients are active for further treatment, and Women and Children Health Center will offer 20% discount on surgical treatment for those with positive screening outcome."*—Liaoning Province

Cost

China's national two-cancer screening program stipulates that the standard of cervical cancer screening subsidy should be no <49.6 yuan per person. An insufficient part of funds will be supplied by provincial, municipal, and county financial departments in a certain proportion; besides, the HPV pilot project has additional subsidies. The actual screening funds in various regions are composed of subsidies provided by the government and self-raised by appointing medical institutions. The number of subsidies varies from place to place ranging from 49.6 to 69 yuan/person except for Shanghai, where screening funding is higher than in other regions due to an additional 227.6 yuan/person (including funds for breast cancer screening) provided by the municipal government for the regional "two-disease screening project".

All regions reported an insufficiency in screening funding, mainly caused by the following reasons: Firstly, cervical cancer screening subsidies are based on the cost of screening technology, leaving out funds for publicity, personnel, and equipment upgrades. Secondly, cervical cancer subsidies are distributed based on the task volume reported on the ground survey; however, the actual number of people who participate in the screening often exceeds the target number. Lastly, in several places, the screening method must be updated, resulting in an increase in screening costs, but the subsidy remains unchanged.

Maintenance

Maintenance refers to the persistence of the program after some time. We mainly focus on the persistence at the setting level and the degree of institutionalization of the project.

Since the launch of the cervical cancer screening project, local governments have introduced relevant policies based on national requests and local economic and medical conditions,

and continuously adjusted and improved them. Simultaneously, a special fund was established to ensure that poor women continued to participate in examinations and treatments.

> *"Both provincial and county levels have their policy documents adjusted according to actual local conditions. The working mechanism is relatively flexible."*—Anhui Province
>
> *"There are very few cases that patients can't afford the medical expenses, because cervical cancer is considered as a major disease and large part of treating expense will be reimbursed by national insurance."*—Shanghai

However, some interviewees claimed that the screening documents were not updated promptly or that the targeted age group of NACCSPRA was inconsistent with those required by the regional project such as Shanghai's "two diseases" (gynecological diseases and breast diseases) program, which will confuse some implementors.

> *"The documents have not been adjusted since 2015, and there are contradictions between screening documents and updated guidelines. For example, experts advocate HPV as the first choice for cervical cancer screening, but it will bring an economic burden if HPV is added. In addition, Shanghai's "two diseases project" requested women under 70 years old to be screened, however, the two-cancer screening only requires women under 64 years old to be screened, so how to deal with the 64–70 age group?"*—Shanghai

Discussion

We select representative areas in China and use the RE-AIM framework to conduct a comprehensive process evaluation of the NACCSPRA, exploring barriers and facilitators during the implementation process. Cost is an important focus of the dimension Implementation, and multiple areas reported a shortage of screening funds. Insufficient investment in the prevention and control of cervical cancer [18] is related to small screening coverage of women of the right year, deficiency in medical equipment and infrastructure, difficulties in construction of large-scale information systems, and inability to promote HPV vaccines [19, 20]. Also, it was reported in various regions that poor welfare of implementation staffs caused by insufficient funding has undermined staffs' working enthusiasm, which may affect screening quality. Capital is of vital importance for the successful implementation of a project, however, it is unavoidable that only limited funding and resources can be invested into one project, as a result, the strategy for funding usage plays a crucial role. According to studies, population coverage is more important than the frequency of screening, so even with the current budget China can reach the elimination goal earlier by reducing the frequency of screening in exchange for extending screening coverage

and increasing HPV vaccine coverage at the same time (7). In addition, repeated tests caused by free screening projects implemented along with unrestricted opportunistic screening might waste social resources and bring a greater financial burden (21, 22). As a result, reducing the number of repeated tests and developing a better screening strategy can alleviate the shortage of funds while also improving the prevention effect.

High adoption was reported at the setting level, government report shows that cervical cancer screenings currently covered 2,644 counties (cities, districts) in China, accounting for 87% of the total. There are differences in the degree of cooperation among medical institutions among different regions. Perceived cooperation levels may not be accurate because they are reflections with no objective evaluation standard. However, further clarification of responsibilities, improved inter-agency communication, and the establishment of an accountability mechanism are all essential. At the staff level, working activity can be stimulated by improving working benefits and environment, and establishing individual performance appraisals.

However, while the proportion of regions that adopted the policy is high, the screening coverage rate is still not high in China. The possible reasons are as follows: Firstly, the main population reached by the project is limited to women with rural household registration or subsistence allowances. Women not covered mainly screened by occupational physical examination and hospital opportunistic testing, however, outpatient screening services are not covered by medical insurance in some regions due to different medical insurance policies across China, which may negatively affect screening coverage rate. Considering that rural women have a relatively lower willingness to receive screening (23) and a higher HPV infection rate (24), under limited medical resources, this strategy for coverage is reasonable. Nevertheless, when compared with the target population in high-income countries such as Australia and Sweden, coverage of NACCSPRA in China is insufficient. And the study has shown that organized programs targeting a small portion of women cannot effectively reduce medical inequality (21, 22). Therefore, China must carry out a wider-scale screening project to reach the goal of 70% of women screened set up by WHO. Secondly, the screening program is not able to reach the entire target population. Deficient management of the floating population is an important factor for screening leakage. The mobile population's willingness to participate will be reduced as they have to pay for screening or return to their registered residence to receive free screening in most areas (25). Special management methods for the mobile population should be developed so that eligible women can be screened in current residence instead of registered ones. In addition, consistent with other studies, specific demographic characteristics and insufficient knowledge and awareness of cervical cancer also affect participation, especially in remote areas (23, 26–29), demonstrating the importance of paying attention to regional differences and population characteristics during project publicity as well as increasing the intensity and professionalism of project publicity (30, 31).

When discussing about the dimension of effectiveness, positive impact of the program was widely acknowledged by providers, which was consistent with previous studies (32). Although there may be negative effects on patients such as psychological pressure and stigma, the overall benefits far outweigh the disadvantages, early diagnosis and treatment have a positive impact on the long-term quality of life of patients.

Among different perspectives of implementation, there are disparities in screening methods, information network level, and capital investment in various regions. Cost and effect must be carefully considered when choosing screening methods. We found that most areas in China are transitioning from pap smear tests to TCT, but only HPV test pilot areas are conducting joint screening methods (HPV test+ cytological test). HrHPV testing has proven to be an effective primary screening method with high sensitivity (33–35), Netherlands, Turkey, and some other countries have already implemented HPV testing nationwide (36). Taking into account differences in regional development, China can adopt a diversified screening strategy and gradually transition to joint screening. HPV testing combined with cytological testing applies to economically developed areas (37); areas with poor resources can continue to use pap smear tests or apply AI-assisted TS technology (38, 39) and HPV self-sampling (40–42).

A comprehensive information system is critical for preventing screening leakage or repetition, improving screening results utilization, and improving inter-institutional cooperation efficiency. Currently, the cancer registry system in China is relatively complete, but the screening information system undergoes insufficient and uneven development among different regions. The main problems with screening information systems in China are as follows: the first one is the limited scale of information systems and the unavailability of information exchange between systems; the second is that information registration in most areas is limited to positive screening results, but previous screenings records (including screening time and results), HPV vaccination status are not contained. The third is the lack of interactivity of information systems at both hospital and patient levels. Both doctors and patients themselves cannot retrieve their previous screening records through the system. However, in the high-income countries, a unified electronic screening registration system and complete follow-up services have normalized (43, 44). Specialized applications for cervical cancer screening projects are being continuously developed (45, 46). This is especially important in China, where regional disparities and a lack of physician resources persist and suggests that the development of a national-wide information platform should be accelerated to achieve the goal of informatization of each process and establish an interactive "patient-platform-hospital" connection.

Although the completion rate of follow-up is high, attention should still be paid to individuals lost to follow-up. Wang et al. showed that the highest missing rate occurs during the process of calling back cytology-positive individuals to participate in colposcopy examination, leading to the loss of high-risk patients (47), which may cause the adverse outcome of disease (48). Possible reasons for loss of follow-up are missing data, diagnostic errors, and substandard quality control (47). The establishment of information systems with interactive functions can promptly remind individuals with positive screening outcomes to check the result and participate in subsequent diagnosis and treatment and make it possible for high-standard quality control and data inspection.

Maintenance of the screening program are ensured by national policy and regional characteristic projects, local departments implement the project in accordance with the policy documents issued by the National Health and Family Planning Commission and the National Women's Federation. At the setting level, timely adaption is important for sustainability of the program, so it is necessary to ensure timely adjustment of screening plan documents to make them match with developed regional screening capacity, changed expert guidelines, and the latest research progress on cervical cancer prevention and control. For example, Shanghai implemented regional characteristic "two diseases" program, which expanded screening disease categories and expanded age range of target population to 70 years old. However, the two programs are often combined in practice due to the overlapping of most examinations, making implementors confused about age range of target group to notify. Therefore, for better sustainability of the program, not only adaption is needed, but highlighting and clearly clarifying any adaption made during intervention to implementors is also indispensable. At the same time, to maintain individual benefits, it is necessary to construct convenient information access. Some countries publish screening information on a unified website timely, for example, the American Society of Colposcopy and Cervical Pathology (ASCCP) (49) simultaneously updates the latest screening information on both web pages and special applications. China can also summarize useful information about cervical cancer and screening programs on a specific website for participants to check in time, thus increasing the initiative of participation. On the other hand, maintaining individual benefits requires improving the ability for subsequent diagnosis and treatment, as well as providing financial assistance to women with financial difficulties.

Strength and limitation

Currently, the RE-AIM framework is only used in a few studies to evaluate cervical cancer screening programs worldwide, and most of them are quantitative studies (12, 13).

The importance of qualitative research, on the other hand, cannot be overlooked when using the RE-AIM framework (17). This study is the first qualitative study using the RE-AIM framework to evaluate cervical cancer screening projects in China, digging into why and how evaluation results were generated through the experience and opinions of project providers. On another hand, semi-structured interviews allowed exploration of unintended results, discovering barriers and facilitators in project implementation through providers' rich and contextualized expressions.

There are also limitations in our study. Firstly, due to the research scale's limitations, only 8 provinces or cities (regions) in China were selected for this study. But uneven regional development in China and disparities in screening coverage between regions (23) were taken into account during sampling by selecting regions in the divided eastern, southern, western, northern, and middle areas in China respectively as research objects. The representativeness of research objects makes up for the small sample size to a certain extent. Secondly, in our research, we discovered a variety of implementation barriers. Nevertheless, due to limitations of the RE-AIM framework itself, we cannot accurately assess the precise impact of each dimension on the screening effect, and further quantitative research is needed. Thirdly, this study used province as a sampling unit. However, during the interview, we found there may be differences in project implementation among different districts even in the same province. We suggest further research in representative regions using smaller administrative divisions as sampling units for more precise results.

Conclusion

The study found barriers and facilitators of NACCSPRA perceived by projects providers. Our study found that shortage of funds is an important problem faced by current screening project, which negatively influences the upgrade of screening strategy, implementors' working environment, etc., thus affecting the screening effect. At the same time, the financial problem also hinders the scale-up and completion of information systems and improvement of interactivity, which reduces the efficiency of screening. In addition, defects in population coverage and allocation of financial resources also deserve attention. In order to achieve optimal resource allocation and screening effectiveness under limited resources, future research on the cost-effectiveness of screening implementation plans in contextualized settings will be required.

Data availability statement

The datasets generated for this study are not publicly available due to concerns for participants' privacy, but are available on reasonable request to the corresponding author.

Ethics statement

Author contributions

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Conflict of interest

Publisher's note

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The association between cigarette smoking and health care service utilization among middle-aged and elderly adults in China

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Objective: To assess the associations between tobacco use and health care service utilization in Chinese individuals aged more or equal to 40 years old.

Method: This research was a cross-sectional study using data from eight provinces in China, and the final sample consisted of 4,733 observations (4,749 participants) aged more or equal to 40 years old. The dependent variable was health care utilization measured by outpatient and inpatient service utilization. Descriptive statistics were used to summarize the socio-demographic characteristics of the sample according to smoking status. The association between tobacco use and health care service utilization was examined by an instrumental variable (IV) probit model.

Results: Of the respondents interviewed in 2020, 3,116 (65.84%) were never smokers, 654 (13.82%) were smokers with the smoking index (SI)<400, and 963(20.34%) were smokers with SI≥400. Smokers with SI<400 reported a 6.80% higher probability of using outpatient services. Smokers with SI<400 and SI≥400 reported a 3.10 and 4.20% higher average probability of using ≥3 outpatient visits than never smokers, respectively. Additionally, smokers with SI<400 and SI≥400 reported a 6.30 and 6.20% higher average probability of using inpatient services than those who had not smoked. Moreover, smokers with SI≥400 were more likely to have had ≥2 hospital visits than nonsmokers.

Conclusions: Smokers make greater use of health care services. Control of smoking may ease the burden of related health care utilization.

Introduction

The tobacco epidemic has become a public health problem around the world that endangers public health and causes severe health and economic consequences. Tobacco was responsible for 8.71 million deaths in 2019. In addition, the global burden of disease study has shown that if tobacco consumption could be stopped, it could have potentially prevented 15% of the deaths that occurred globally in 2019 (1). Furthermore, the

economic burden related to tobacco is rising. Goodchild et al. demonstrated that the direct economic cost of smoking-attributable diseases in 2012 accounted for 5.7% of global health expenditures (2).

China is the largest manufacturer and consumer of cigarettes worldwide (3). A study investigated the prevalence of tobacco smoking among Chinese, and their results showed that 62.4% of Chinese adult men reported histories of smoking in 2010; specifically, 54% of them were current smokers, and only one-third of these current smokers intended to quit (4). Tobacco consumption results in approximately one million deaths in China (5). Moreover, the economic burden of smoking-attributable diseases worldwide is substantial, and it is the same in China. A systematic review of 20 studies related to the economic burden of smoking-attributable disease in China indicated that the estimated total cost of smoking ranged from 57 to 368 billion RMB; specifically, outpatient visits accounted for up to 98% of the direct costs (6). Moreover, Yang et al. performed a pooled meta-analysis to explore the trend of tobacco smoking in various regions and showed that the smoking prevalence rate for male ever-smokers continues to increase in China; in addition, they reported that current smoking was associated with the risk of death (7). In general, these findings indicate that China is facing a dilemma of sustained increases in the health burden of tobacco.

The fast aging population and the increased prevalence of chronic diseases are current health care challenges China faces (8–12). Smoking is a preventable risk factor for various diseases, including cardiovascular disease, lung cancer, diabetes, and chronic respiratory disease (13–15). Additionally, smoking accelerated the epidemic of noncommunicable chronic diseases in China (16–18). Therefore, to reduce the tobacco-attributable disease burden and allocate health service resources effectively, it is necessary to assess the effect of smoking on health care utilization.

Various studies have investigated the impact of tobacco consumption on the use of outpatient services. Kahende et al. explored smoking status differences in health care utilization from a large population. They found that current and former smokers who had quit for < 2 years were more likely to have outpatient visits than never smokers after controlling for various factors (19). This finding was also reported by Li et al. using a Chinese population (20). On the other hand, a study from Azagba et al. reported conflicting results. The authors divided participants into two groups—low and high users; they found no association between higher utilization of general practitioners, specialists, and current smokers in the group of low users, and current smokers had fewer hospital visits than never smokers (21). In addition, many studies have reported the effect of smoking on inpatient care utilization. Researchers have found that, current and former smokers are more likely to use hospitalization services than people who have never smoked; additionally, smoking is strongly associated

with increased use of hospital services (19, 21–23). Although China is the largest manufacturer and consumer of cigarettes, there are few studies estimated the impact of cigarette smoking on health care utilization among the Chinese population. In addition, it is necessary to focus on middle-aged people because there is evidence that smoking's cumulative influence on health can impact middle-aged people more for the utilization of health care services due to smoking-attributable disease than young people (24). In addition, previous studies have demonstrated methodological limitations, especially in cross-sectional data, and studies have commonly reported endogeneity problems. Additionally, whether to become a smoker is the result of individual self-selection. Endogeneity problems caused by omitted variables may result in a biased estimation. Hence, to control for endogeneity, the instrumental variable (IV) technique is commonly used (25, 26).

Therefore, the present study aimed to assess the associations between tobacco use and health care service utilization among Chinese individuals aged more or equal to 40 years old using an instrumental variable (IV) probit model. We hypothesize that smoking is positively associated with health care service utilization.

Materials and methods
Study design

We conducted a household survey from November 1, 2019, to January 30, 2020. Participants were Chinese individuals aged more or equal to 40 years old from 24 primary health care facilities (PHC). A stratified multi-stage sampling method was taken. Firstly, we selected eight province-level regions (Hebei, Heilongjiang, Shandong, Henan, Shanxi, Hubei, Sichuan, Guizhou) according to the level of economic development. Then, we randomly selected 2–4 PHC institutions in each province as our investigation units. Approximately 100 households of each PHC were chosen randomly. The inclusion criteria were as follows: the head of the household has a minimum of 40 years, lived in the area for at least half a year, and was willing to participate in the study. For observational studies involving logistic regression in the analysis, a minimum of 500 sample size is recommended to derive statistics that represent the parameters of the target population (27). Therefore, with eight provinces selected in the research, this observational study needed at least 4,000 participants. After eliminating 16 missing data about family income, the final sample consisted of 4,733 observations aged more or equal to 40 years old (4,749 participants).

In this study, participants had face-to-face interviews with data collectors, who had received adequate training to ensure the reliability of the survey. They used validated questionnaires that includes general household information, basic demographics,

TABLE 1 The definition and abbreviation of selected variables in the study.

Variable	Abbreviation	Definition
Smoking index	SI	Categorical variable scored 1 if $0<SI<400$, 2 if $SI\geq400$, and 0 if respondents were never smokers.
Outpatient service utilization	Outpatient	Binary variable scored 1 if respondents had outpatient visits in the past year and 0 otherwise
Number of outpatient visits ≥3	-	Binary variable scored 1 if respondents had outpatient visits ≥3 times in the past year and 0 if respondents had an outpatient visit
Inpatient service utilization	Inpatient	Binary variable scored 1 if respondents had hospital admissions in the past year and 0 otherwise
Number of times hospitalized ≥2	-	Binary variable scored 1 if respondents had hospital admissions ≥2 times in the past year and 0 if respondents had a hospital admission
Age	Age	Continuous variable measured in years
Gender	Gender	Binary variable scored 1 for males and 0 for females
Educational level	Education	Categorical variable scored 1 for Illiterate, 2 for Primary School, 3 for Middle School, 4 for High School and Junior College, and 5 for College and above
Marital status	Marriage	Categorical variable scored 1 for Single, 2 for Married, and 3 for Divorced or Widowed
Logarithm of family income	Lnincome	Continuous variable
Residence location	Residence	Binary variable scored 1 for rural and 2 for urban
Work status	Work	Binary variable scored 1 for employed people, 0 for Unemployed people
Health insurance	Insurance	Binary variable scored 1 for insurance covered, 0 for no insurance covered
Health status	Health status	Binary variable scored 1 for at least one chronic disease, 0 for no chronic diseases.
Drink	Drink	Binary variable scored 1 if respondents had drinking habits and 0 otherwise
Whether the increase in the price of cigarettes reduced smoking	PRS	Binary variable scored 1 if the increase in cigarette prices reduced the number of cigarettes smoked and 0 otherwise

smoking behavior, health status, health care utilization and health insurance, and household economy. The Cronbach's alpha of the questionnaire was 0.775. There was a contact person in each investigation unit who was under the leadership of the research team. The contact person checked all the questionnaires before handing over to the research team. Then, the research team double-checked all the questionnaires and made phone call to participants if necessary. We obtained informed consent from all the participants prior to the enrollment. This study received approval from the ethics committee of the Capital Institute of Pediatrics, Beijing (ID: SHERLL2020017).

Measures

Dependent variables

The study measured health care utilization by outpatient and inpatient service utilization. We obtained data by asking "How many times have you seen a doctor during the past year," and "How many times have you been hospitalized during the past year." Outpatient service utilization and inpatient service utilization were binary variables coded 1 if participants have used health service at least once and 0 otherwise. Moreover, the number of outpatient visits and hospital admissions were grouped into two levels. This cut-off point was chosen because approximately half of the participants had ≥3 outpatient visits and ≥2 hospitalizations. Details of the definition of dependent variables were shown in Table 1.

Independent variables

In the current study, we focused on cigarette smoking. Respondents were asked "Do you smoke now?." The corresponding options were: (1) No, (2) Yes, and (3) Have quit smoking. Respondents who answered option (1) were classified as never smokers. Respondents who reported option (2) or (3) were asked additional questions about smoking history and amount. The smoking index (SI) was adopted and was defined as the root number of cigarettes smoked every day multiplied by the smoking years (28). Then, the cigarette smoking was categorized as never smokers, SI<400, and SI≥400.

TABLE 2 Description of the selected samples of Chinese adults ≥40 years old by smoking status (N = 4,733).

Characteristics	Smoking status			p-value
	Never smoked	**SI < 400**	**SI ≥ 400**	
	N(%)/Mean	N(%)/Mean	N(%)/Mean	
Age	55.26 ± 11.02	57.55 ± 13.01	57.34 ± 10.51	<0.001
Gender				<0.001
Male	1,067 (43.66)	462 (18.90)	915 (37.44)	
Female	2,049 (89.52)	192 (8.39)	48 (2.09)	
Marital status				<0.001
Single	52 (45.61)	21 (18.42)	41 (35.97)	
Married	2,767 (66.85)	538 (13.00)	834 (20.15)	
Divorced/Widowed	297 (61.88)	95 (19.79)	88 (18.33)	
Education				<0.001
Illiterate	419 (66.61)	115 (18.28)	95 (15.11)	
Primary school	748 (62.86)	158 (13.28)	284 (23.86)	
Middle school	1,052 (66.12)	176 (11.06)	363 (22.82)	
High school/junior college	500 (65.96)	112 (14.77)	146 (19.27)	
University/college and above	374 (69.91)	89 (16.64)	72 (13.45)	
Work				<0.001
No	1,007 (68.36)	241 (16.36)	225 (15.27)	
Yes	2,109 (64.69)	413 (12.67)	738 (22.64)	
Lnincome	10.79	10.64	10.50	0.520
Residence location				<0.001
Rural	2,060 (64.47)	423 (13.24)	712 (22.29)	
Urban	1,056 (68.67)	231 (15.02)	251 (16.31)	
Health insurance				0.626
No	65 (67.71)	15 (15.63)	16 (16.66)	
Yes	3,051 (65.79)	639 (13.78)	947 (20.42)	
Health status				<0.001
0	2,231 (70.09)	349 (10.96)	603 (18.95)	
1	885 (57.09)	305 (19.67)	360 (23.24)	
Drink				<0.001
No	2,512 (76.17)	363 (11.01)	423 (12.29)	
Yes	604 (42.09)	291 (20.28)	540 (37.63)	
Total	3,116 (65.84)	654 (13.82)	963 (20.34)	

Covariates

The covariates included economic status (logarithm of household income), medical insurance schemes, individual characteristics (gender, age, marital status, educational level, working status, residence location), drinking habits, and health status (hypertension, diabetes, chronic obstructive pulmonary disease, coronary heart disease, stroke, and cancer). Definitions of all relevant variables are provided in Table 1.

Instrumental variable

We used whether the increase in cigarette prices reduced smoking as an instrumental variable (29).

Data analysis

The challenge of this study is to overcome endogeneity problems existed in observational studies and we adopted an instrument variable (IV) probit model to control for potential endogeneity problems. The instrumental variable was whether the increase in the price of cigarettes reduced smoking. It was associated with smoking behavior but did not directly affect health care service utilization, therefore fulfilling the instrumental variable exogeneity requirement. The IV probit model was adjusted for gender, age, marital status, education, working status, economic status, medical insurance schemes, health status, and drinking habits.

To further estimate the average treatment effect on the treated (ATET) of smoking on health care service utilization, we performed marginal analysis using the parameter estimates from the IV probit model. ATET is the estimated average difference of the treatment and control potential outcomes in the treated population. It can help obtain interpretable effects when the coefficient estimates are not directly useful.

The IV probit model is constructed as follows:

$$utilization_i = \begin{cases} 1 \ if, \ utilization_i^* > 0 \\ \\ 0 \ if, \ otherwise \end{cases} \tag{1}$$

$$utilization_i^* = \beta_1 Smoke_i + \gamma Z + \mu_i \tag{2}$$

$$Smoke_i = \pi_1 Z + \pi_2 I + \alpha_i \tag{3}$$

$utilization_i$ refers to the health care service utilization of the respondents. $utilization_i^*$ is the latent variable of health care service utilization in Equation (1). $Smoke_i$, the independent variable of interest. β_1 is the coefficient of interest. It captures the estimated effect of smoking on health care service utilization. Z is a rich set of individual characteristics; I is the instrumental variable; γ, π_1 and π_2 are the vectors of parameters for the control variables; μ_i and α_i are the error terms in the equation; and i denotes an individual respondent.

All analyses were performed by Stata 17.0 (Stata Corp, College Station, TX, USA), and the statistical significance was set at P < 0.05.

Results

Sample characteristics

Table 2 shows the distribution of demographic characteristics of never smokers, SI<400, and SI≥400. Of

TABLE 3 Probit regression analysis and IV probit regression analysis of outpatient service utilization.

	Outpatient service utilization			
	Visit (Y/N)		Number of outpatient visits (≥3 times)	
	Probit (i)	IV Probit (ii)	Probit (iii)	IV Probit (iv)
Smoking index (reference group: Never smoked)				
SI<400	0.185** (0.060)	0.165** (0.069)	0.110 (0.084)	0.221* (0.095)
SI≥400	0.107 (0.056)	0.091 (0.089)	0.075 (0.085)	0.272* (0.127)
Age	0.008*** (0.002)	0.008*** (0.002)	0.017*** (0.003)	0.017*** (0.003)
Gender (reference group: Female)				
Male	0.025 (0.047)	0.044 (0.046)	0.172** (0.071)	0.189** (0.072)
Education level (reference group: Illiterate)				
Primary school	−0.051 (0.067)	−0.081 (0.067)	0.043 (0.075)	−0.008 (0.089)
Middle school	−0.084 (0.069)	−0.159 (0.068)	−0.069 (0.080)	−0.016 (0.095)
High school/junior college	−0.133 (0.081)	−0.319 (0.078)	−0.125 (0.098)	0.058 (0.118)
University/college and above	−0.150 (0.097)	−0.447 (0.090)	−0.203 (0.127)	0.071 (0.147)
Marital status (reference group: Single)				
Married	−0.171 (0.130)	−0.154 (0.126)	0.026 (0.155)	−0.023 (0.175)
Divorced/widowed	−0.003 (0.143)	−0.051 (0.139)	−0.025 (0.168)	−0.153 (0.191)
Residence location (reference group: Rural)				
Urban	−0.376*** (0.048)	−0.255*** (0.049)	−0.027 (0.062)	−0.033 (0.072)
Lnincome	−0.019 (0.023)	−0.025 (0.023)	−0.042 (0.028)	−0.016 (0.029)
Work (reference group: No)				
Yes	0.047* (0.045)	0.042 (0.046)	−0.074 (0.063)	−0.073 (0.065)
Health insurance (reference group: No insurance)				
Insurance	−0.257 (0.137)	−0.255 (0.132)	−0.232*** (0.054)	−0.518*** (0.180)
Health status (reference group: No chronic disease)				
1	0.652*** (0.044)	0.652*** (0.044)	0.738*** (0.051)	0.514*** (0.063)
Drink (reference group: no drink)				
Drink	−0.123* (0.047)	−0.122* (0.047)	−0.083 (0.060)	0.028 (0.072)
_cons	−0.031 (0.324)	−0.041 (0.329)	−0.776 (0.492)	−0.842* (0.441)
N	4,733	4,733	4,733	4,733

Standard errors in parentheses. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

the respondents interviewed in 2020, 3,116 (65.84%) were never smokers, 654 (13.82%) were smokers with SI<400, and 963(20.34%) were smokers with SI≥400. The average ages of SI<400 and SI≥400 were 57.55 ± 13.01 and 57.34 ± 10.51, respectively. Never smokers tended to be younger than smokers. Never smokers (43.66%) included a higher proportion of males than smokers with SI≥400 (37.44%) and smokers with SI<400 (18.90%). There were significant differences in marital status ($p < 0.001$), educational status ($p < 0.001$), work status ($p < 0.001$), residence location ($p < 0.001$), health status ($p < 0.001$), and drinking habits ($p < 0.001$) while the logarithm of family income ($p = 0.520$) and health insurance ($p = 0.626$) were not significant.

The association between smoking and health care service utilization

Columns (i) and (iii) of Table 3 present the results of the probit regression model (outpatient care utilization). After controlling for smoking index, age, sex, marital status, education, income, residence, health insurance, health status, and drinking habits, smokers with SI<400 increased the probability of having an outpatient visit by 18.50% ($p < 0.001$). Smoking was positively related to the number of outpatient visits, while the results are not significant ($p > 0.05$).

Column (ii) and (iv) of Table 3 report the estimated results of the IV probit regression model. The estimated coefficient

TABLE 4 Probit regression analysis and IV probit regression analysis of inpatient service utilization.

	Inpatient service utilization			
	Hospitalization (Y/N)		Number of times hospitalized (≥2 Times)	
	Probit (i)	IV Probit (ii)	Probit (iii)	IV Probit (iv)
Smoking index (reference group: Never smoked)				
SI<400	0.221*** (0.070)	0.267*** (0.080)	0.075 (0.093)	0.143 (0.110)
SI≥400	0.175*** (0.069)	0.263* (0.103)	0.190* (0.094)	0.309* (0.141)
Age	0.012*** (0.002)	0.012*** (0.003)	0.008*** (0.004)	0.009*** (0.003)
Gender (reference group: Female)				
Male	−0.007 (0.060)	−0.001 (0.061)	0.015 (0.081)	0.031 (0.082)
Education level (reference group: Illiterate)				
Primary school	0.043 (0.075)	0.043 (0.076)	−0.061 (0.096)	−0.049 (0.092)
Middle school	−0.069 (0.080)	−0.066 (0.081)	−0.144 (0.104)	−0.117 (0.100)
High school/junior college	−0.125 (0.098)	−0.124 (0.100)	−0.229 (0.133)	−0.175 (0.125)
University/college and above	−0.203 (0.126)	−0.198 (0.127)	−0.187 (0.169)	−0.092 (0.157)
Marital status (reference group: Single)				
Married	0.025 (0.155)	0.023 (0.153)	0.257 (0.222)	0.244 (0.208)
Divorced/widowed	−0.025 (0.168)	−0.025 (0.168)	0.124 (0.236)	0.123 (0.229)
Residence location (reference group: Rural)				
Urban	−0.027 (0.062)	−0.028 (0.062)	0.113 (0.083)	0.112 (0.079)
Lnincome	−0.042 (0.028)	−0.039 (0.028)	−0.078* (0.037)	−0.076* (0.037)
Work (reference group: No)				
Yes	−0.232*** (0.054)	−0.232*** (0.054)	−0.267*** (0.072)	−0.268*** (0.070)
Health insurance (reference group: No insurance)				
Insurance	0.145 (0.193)	0.145 (0.211)	0.007 (0.262)	0.006 (0.301)
Health status(reference group: No chronic disease)				
1	0.738*** (0.052)	0.738*** (0.051)	0.820*** (0.072)	0.819*** (0.067)
Drink (reference group: no drink)				
Drink	−0.083 (0.060)	−0.081 (0.061)	−0.167* (0.084)	−0.167* (0.083)
_cons	−1.594*** (0.411)	−1.649*** (0.415)	−1.69** (0.548)	−1.76*** (0.555)
N	4,733	4,733	4,733	4,733

Standard errors in parentheses. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

reported positive and significant associations between smoking and the number of outpatient visits ($p < 0.05$).

As shown in Table 5, the ATET of 0.068 shows that for smokers with SI<400, the average probability of outpatient utilization would be 6.80% higher than if they had not smoked ($p < 0.01$). The ATET of 0.031 and 0.042 indicates that for smokers with SI<400 and SI≥400, the average probability of having higher outpatient service utilization would be 3.10% ($p < 0.05$) and 4.20% ($p < 0.05$), respectively higher than if they had not smoked.

Columns (i) and (iii) of Table 4 present the results of the probit regression model (inpatient care utilization). After controlling for smoking index, age, sex, marital status, education, income, residence, health insurance, health status, and drinking habits, smokers with SI<400 and SI≥400 increased

the probability of having a hospital admission by 22.10% ($p < 0.001$) and 17.50% ($p < 0.001$), respectively. Smokers with SI≥400 were positively associated with the number of hospitalizations ($p < 0.05$).

Columns (ii) and (iv) of Table 4 present the estimated results of the IV probit regression model. The estimated coefficient results show that smoking positively affects hospital admissions, and smokers with SI≥400 were related to the number of times hospitalized.

As shown in Table 5, the estimated ATET implies that smokers reported approximately 6.20% higher average probabilities of using inpatient services than never smokers. The ATET of 0.051 shows that for smokers with SI≥400, the average probability of higher hospital admissions increased by 5.10% when SI≥400 vs. never smokers ($p < 0.05$).

TABLE 5 Estimated ATET of smoking on outpatient service utilization and inpatient service utilization.

	Margin	Unconditional Std. Err.	z	P>z	[95% Cl]	
ATET						
Outpatient service utilization (Y/N)						
(SI<400 vs. never smoked)	0.068	0.023	2.87	0.004	0.021	0.115
(SI≥400 vs. never smoked)	0.043	0.031	1.38	0.169	−0.018	0.104
Number of outpatient visits (≥3 Times)						
(SI<400 vs. never smoked)	0.031	0.015	2.11	0.035	0.002	0.059
(SI≥400 vs. never smoked)	0.042	0.028	2.00	0.046	0.000	0.082
Inpatient service utilization (Y/N)						
(SI<400 vs. never smoked)	0.063	0.019	3.21	0.001	0.024	0.100
(SI≥400 vs. never smoked)	0.062	0.025	2.45	0.014	0.012	0.110
Number of inpatient visits (≥2 Times)						
(SI<400 vs. never smoked)	0.017	0.013	1.26	0.207	−0.009	0.044
(SI≥400 vs. never smoked)	0.051	0.020	1.99	0.046	0.000	0.080

TABLE 6 Effect of smoking on outpatient service utilization and inpatient service utilization among different age groups.

	N in sample	Outpatient service utilization (Y/N)	Inpatient service utilization (Y/N)
40–49 years	1,663		
Never smoked	1,185		
	(reference)		
SI<400	228	0.257* (0.105)	0.070 (0.169)
SI≥400	250	0.092 (0.107)	0.259 (0.165)
50–59 years	1,441		
Never smoked	907 (reference)		
SI<400	171	0.203 (0.116)	0.519*** (0.135)
SI≥400	333	0.015 (0.100)	0.263* (0.130)
60+ years	1,659		
Never smoked	1,024		
	(reference)		
SI<400	225	0.115 (0.097)	0.173 (0.097)
SI≥400	380	0.149 (0.089)	0.105 (0.096)

Standard errors in parentheses. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. All the models were adjusted for economic status, medical insurance schemes, individual characteristics, drinking habits, and health status.

In Table 3, the coefficient for the age indicates that the likelihood of using outpatient services and the number of outpatient visits increase with age ($p < 0.001$). Participants who lived in cities ($p < 0.001$) and had drinking habits ($p < 0.05$) were less likely to have an outpatient visit. Male sex was positively related to increased outpatient visits ($p < 0.01$). The impact of health insurance on increased outpatient visits were negative but significant ($p < 0.001$). Health status was positively associated with outpatient services ($p < 0.001$).

In Table 4, the coefficient for the age indicates that the likelihood of using inpatient services and the number of hospital visits increase with age ($p < 0.001$). Family income ($p < 0.05$) and drinking habits ($p < 0.05$) were negatively associated with the frequency of hospital visits. Health status was positively associated with inpatient services ($p < 0.001$).

Results from Table 6 indicate that, people between the ages of 40 and 49 with SI<400 were 25.70% ($p < 0.05$) more likely to have outpatient services than those who never smoke. People between the ages of 50 and 59 with SI<400 and SI≥400 were 51.90% ($p < 0.001$) and 26.30% ($p < 0.05$) more likely to be hospitalized than never smokers, respectively.

Discussion

Using an IV probit model, we assess the associations between tobacco use and health care service utilization among Chinese individuals aged more or equal to 40 years old. The results support our hypothesis that smoking is positively associated with the utilization of health care services. Specifically, smokers with SI<400 reported a 6.80% higher probability of using outpatient services. Smokers with SI<400 and SI≥400 reported a 3.10 and 4.20% higher average probability of using ≥3 outpatient visits than never smokers. Additionally, smokers with SI<400 and SI≥400 reported a 6.30 and 6.20% higher average probability of using inpatient services than those who had not smoked. Moreover, participants with SI≥400 were more likely to have had ≥2 hospital visits than nonsmokers.

Our findings are consistent with previous studies in other countries, such as the USA (19), Canada (21), Spain (22), Switzerland (30), Denmark (31), Germany (32), South Korea (33) and the Middle East (34). Furthermore, a recent cohort

study from Hubei Province in China suggested that smoking behaviors, such as quitting smoking early and consuming a small amount of cigarettes, would decrease health care utilization and medical costs (10). Apart from hospital admission and the number of hospital visits, research from Hvidtfeldt et al. (31) and Fassmer et al. (32) found that smokers had longer duration stays in the hospital than those who never smoked, which supports the conclusion that smoking elevates health care utilization.

Positive associations between tobacco consumption and health care utilization are biologically plausible, as smoking is considered an important factor for many diseases requiring health care utilization. Many studies have documented the adverse health impacts of smoking, including cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases (13, 15, 35–37). These health risks can result in the use of health services.

We also found that the impact of age on health care utilization may depend on different age groups. For example, the effect of age was positive and significant only in smokers aged 40–59 years, and the effect of age over 60 years was positive but not significant. Given that smoking is the leading cause of premature death in older people (38), there may be a healthy survivor effect in our sample that resulted in dilution of health services for older smokers.

Against the backdrop of an aging population and increasing health expenditures, the findings may have implications to help the government better reach the expected public health outcomes. To reduce the consumption of tobacco products and the tobacco-related disease burden, strongly enforced and comprehensive policies are urgently needed. For example, communities should carry out health education programs and highlight the health risks of smoking to smokers. In the meantime, when carrying out tobacco control activities, local health authorities should focus on middle-aged and elderly people and people with chronic diseases. Moreover, China still needs to continuously raise tobacco taxes and prices to reduce the tobacco consumption and mitigate the financial burden on the government. In addition, developing a tobacco excise tax and earmarking taxes for public health expenditure is necessary, as government spending on tobacco control is believed to be cost-effective.

In this study, the instrumental variable (IV) probit model overcomes the endogeneity problems that previous cross-sectional studies have faced. The estimated results for the IV probit regression model were mostly higher than those for the probit regression model, suggesting that the probit model may have underestimated the impact of smoking on health care use due to selection bias. However, the current study has some limitations that should be emphasized. First,

self-reported data we used in the study may result in recall bias. Second, a cross-sectional design is unlikely to establish a causality between health care utilization and smoking behaviors. Longitudinal data is needed to further assess the cause-and-effect relationship between smoking and health care service utilization.

Conclusion

The findings of this study showed that smoking elevates the use of health care services. This study could provide the government with better information on anti-smoking measures and inform health sector decisions on health care resource allocation. Interventions aiming to reduce smoking have the potential to greatly reduce health service utilization among middle-aged and older Chinese.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: data involves personal privacy issues. Requests to access these datasets should be directed to JS, jrsong1993@163.com.

Author contributions

JS made contributions to study design, developed the methodology, performed the statistical analysis, and wrote the manuscript. CJ developed the methodology and coordinated the analyses. XC developed the methodology, reviewed, and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Identification of high-risk factors for prehospital delay for patients with stroke using the risk matrix methods

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Background: Stroke has become a leading cause of mortality and adult disability in China. The key to treating acute ischemic stroke (AIS) is to open the obstructed blood vessels as soon as possible and save the ischemic penumbra. However, the thrombolytic rate in China is only 2.5%. Research has been devoted to investigating the causes of prehospital delay, but the exact controllable risk factors for prehospital delay remain uncertain, and a consensus is lacking. We aimed to develop a risk assessment tool to identify the most critical risk factors for prehospital delay for AIS patients.

Methods: From November 2018 to July 2019, 450 patients with AIS were recruited. Both qualitative and quantitative data were collected. The Delphi technique was used to obtain expert opinions about the importance of the risk indices in two rounds of Delphi consultation. Then, we used the risk matrix to identify high-risk factors for prehospital delay for AIS patients.

Results: The risk matrix identified the following five critical risk factors that account for prehospital delay after AIS: living in a rural area; no bystanders when stroke occurs; patients and their families lacking an understanding of the urgency of stroke treatment; patients and their families not knowing that stroke requires thrombolysis or that there is a thrombolysis time window; and the patient self-medicating, unaware of the seriousness of the symptoms, and waiting for spontaneous remission.

Conclusions: The risk analysis tool used during this study may help prevent prehospital delays for patients with AIS.

KEYWORDS

acute ischemic stroke, prehospital delay, risk assessment, risk matrix, Borda count

Introduction

Stroke is becoming a significant health burden and one of the leading causes of death worldwide (1). Acute ischemic stroke (AIS), which is the most common type of stroke, accounts for approximately 73–87% of all strokes (2). Evidence indicates that the administration of recombinant tissue-type plasminogen activator (t-PA) is an effective intervention for early treatment of AIS (3). Although t-PA has been approved for stroke treatment for more than 20 years, only 11.1% of patients in developed countries (4) and 2.5% in China (5) eventually receive thrombolytic therapy.

Prehospital delay is determined by when the time from the onset of the incidence until the patient's arrival exceeds 3 h (6). Prehospital delay is the main cause of low thrombolysis rate in patients with AIS (7). Therefore, effective measures are to be taken by healthcare professionals to reduce prehospital delay.

Many factors can contribute to the prehospital delay of patients with stroke, including demographic (e.g., age, sex, education, income), clinical (e.g., symptom etiology, symptoms, clinical history, and timing of symptom onset), and cognitive-behavioral (e.g., symptom recognition and perceived severity) factors (6, 8–10). Various risk factors have been suggested, but controversy persists. Some scholars believed that age does not affect prehospital delay (11–13), whereas others have an opposite opinion. One study have found that prehospital delay is increased for elderly patients (14), whereas other studies have found that elderly patients tend to focus more attention on their condition, thereby reducing the incidence of prehospital delay (15, 16). It has been suggested that the level of education does not affect prehospital delay (11). However, some have argued that the level of education would directly affect the cognition of stroke patients with risk awareness. Therefore, the incidence of prehospital delay is reduced for individuals with higher educational levels (17). In addition, patients with a history of diabetes may have symptoms that mimic autonomic nervous disorders after hypoglycemia, such as limb weakness, unclear speech, sensory disorders, dizziness, and confusion, and other pre-stroke symptoms, which may be misdiagnosed, thus, resulting in stroke prehospital delay (9). Studies have shown that some patients with diseases that require self-management (such as atrial fibrillation) are more likely to detect abnormalities and be more aware of their condition, and less likely to have a delayed response to symptoms (18). Additionally, studies have not yet reached a unified conclusion regarding the role of the timing of symptom onset in prehospital delay. One study pointed out that during the daytime, patients are conscious and can identify their abnormalities immediately (12). Accordingly, during the night, when patients are asleep, the detection of the onset of symptoms is relatively more likely to be delayed. However, some scholars have had different opinions; for example, one study indicated that because there is less traffic at night, patients can travel to the hospital faster and receive timely treatment after symptom onset (19). Therefore, prehospital delay for stroke patients depends on many controversial factors that can occur at any stage before the arrival of the patient at the hospital (20). Research has been devoted to investigating the causes of prehospital delay, but the exact controllable risk factors for prehospital delay remain uncertain, and a consensus is lacking. One key barrier to prehospital delay prevention is the lack of risk assessment tools to evaluate existing or potential prehospital delay risks. The availability of a highly accurate risk assessment tool would facilitate proactive identification of individuals in need of more intensive monitoring and proper intervention. Therefore, risk management approaches can be used to address this problem.

Prehospital delay risk management is not only the management of a single risk factor of prehospital delay in the past, but also the integrated management of all risks from the perspective of the whole system. This study systematically sorted out and screened various risk factors leading to stroke prehospital delay from the levels of patients, their families, and emergency systems, and identified the key risk factors leading to stroke prehospital delay. Identifying the hierarchical importance of risk factors for prehospital delay may help healthcare professionals effectively identify people at high risk and provide appropriate interventions. This method can prevent prehospital delay and allow for efficient utilization of healthcare resources.

The objective of this study was to develop a risk assessment tool to estimate and stratify the critical risk factors for prehospital delay. A univariate analysis was used to obtain important risk indicators of prehospital delay for stroke patients. The Delphi method was utilized to obtain experts' opinions regarding scoring the impact and occurrence possibilities of these risk indices to quantify agreement among experts regarding their level of importance. After two rounds of expert consultation, a risk matrix was constructed according to the quantitative results of each risk factor. The Borda count method was used to calculate the weight allocated to each of the final risk indices. The risk matrix method combined with the Borda count method comprehensively evaluates risk classes and avoids risk ties.

Methods

Sample size calculation

The sample size was calculated using a sample size formula for a descriptive cross-sectional study: $n = Z\alpha^2 p \, (1 - p)/d^2$, where n is the minimum desired sample size, $Z\alpha$ is the standard normal deviation (usually set as 1.96) that corresponds to a 5% level of significance, p is the prevalence, and d is the degree of accuracy (precision). Previous studies have shown that the incidence of prehospital delay for stroke patients was 60% (21); therefore, d was set at 5%, and $n = 1.96^2 \times 0.6 \times (1 - 0.6)/0.05^2 = 369$. After anticipating an approximate drop-out rate of 15% during the study course, 450 participants were recruited.

Data collection

This study was approved by a local Institutional Ethics Committee. We included patients who were 18 years or older, admitted to a tertiary hospital between November 1, 2018 and July 31, 2019, had AIS diagnosed by clinical examination and neuroimaging results (at least one computed tomography or magnetic resonance imaging brain scan), and were willing to participate in the present study. The exclusion criteria were patients with transient ischemic attack or cerebral hemorrhage,

TABLE 1 Risk rating scale.

Probability of risk occurrence	Severity of the consequences				
	Negligible	Minor	Moderate	Severe	Critical
Very unlikely	I	I	II	III	III
Less likely	I	II	II	III	IV
Likely	II	II	III	IV	IV
More likely	III	III	III	IV	V
Very likely	III	IV	IV	V	V

cognitive impairment, or inability to answer questions. We also excluded patients whose time from disease onset to admission could not be determined.

Variable measurements

Prehospital delay risk factors

We identified the risk factors for prehospital delay in stroke patients through literature review and qualitative interviews. Based on the review of current evidence, we obtained 59 risk factors related to stroke prehospital delay. In addition, we conducted face-to-face interviews on risk factors of stroke prehospital delay with four patients and their families, two community general practitioners, one emergency physician, eight neurologists, and four emergency center staffs. The content analysis method was used to analyze the interview data, and a total of 35 risk factors were extracted. After excluding repeated risk factors among the results of literature review and qualitative interviews, a total of 64 risk factors were left as the basis for the formulation of the questionnaire. Therefore, the self-designed questionnaire had five sections with 64 items comprising sociodemographic factors, clinical factors, patients' medical decisions, transport factors, and time records. Socioeconomic factors included age, sex, educational level, family income, and type of medical insurance. Clinical characteristics included clinical history, primary symptoms, stroke severity, stroke type, and timing of symptoms. Patients' cognitive-behavioral factors included stroke knowledge, identification of premonitory symptoms, and assessment of symptom severity. Transport factors included the use of emergency medical services and transfer experience. Time records included the time when stroke symptoms were detected, the time when it was decided that medical attention was necessary, and the time of arrival at the hospital.

Identification of aura symptoms

Aura symptoms were identified and assessed using an alertness questionnaire regarding premonitory symptoms of stroke that was developed by Zhang et al. (22). The questionnaire comprises nine items and uses a two-point system: a score of 1 is given for a correct answer and a score of 0 is given for a wrong answer.

Stroke knowledge

The Stroke Knowledge Scale was used to evaluate stroke knowledge. The scale was developed in 2016 by Yao (23) and includes six dimensions (stroke symptoms, first aid measures, risk factors, safe drug use, health behavior, and rehabilitation knowledge). A total of 40 items are scored using a two-point system: a score of 1 is given for the correct answer and a score of 0 is given for the wrong answer or no answer. The total score ranges from 0 to 40.

Delphi consultations

In this study, the selection criteria of the experts were as follows: (a) engaged in stroke medical work; (b) had 5 years or more experience in stroke medical work; and (c) able to understand the content of the questionnaire and implications of the relevant indexes. The questionnaire was sent to the experts by e-mail after receiving their prior approval. The responses of each participant remained anonymous throughout each survey round and were analyzed anonymously. Only team members knew the identifiable responses from each participant. Delphi participants did not know the identities of the other Delphi participants during the Delphi study. Experts then defined the basis of their judgment according to whether their view was based on theoretical knowledge, practical experience, learned from peers, or intuitive feeling (24).

Eighteen experts participated in the consultations; 33.33% were males (6/18) and 66.67% were females (12/18). All experts responded to the two rounds of Delphi questionnaires. They were distributed in Heilongjiang Province, Shandong Province, and Henan Province. Their average age was 42.8 years (range, 32–50 years). Their average professional experience was 15.7 years (range, 6–27 years). Regarding the academic level of the experts, 33.3% (6/18) were professors, 61.1% (11/18) were associate professors, and 5.6% (1/18) were attending physicians.

TABLE 2   Prehospital delay according to patient characteristics ($n = 450$).

Factors	Prehospital delay time <3 h ($n = 57$)	Prehospital delay time ≥3 h ($n = 393$)	*P*-value[a]
Having commercial medical insurance, No. (%)	12 (21.05)	44 (11.20)	0.035[b]
Physical examination status ≥1/year, No. (%)	23 (40.35)	90 (22.90)	0.005[b]
Living in Urban, No. (%)	51 (89.47)	247 (62.85)	<0.001[b]
Family history of stroke, No. (%)	21 (36.84)	94 (23.92)	0.037[b]
Wake-up stroke, No. (%)	0 (0.00)	82 (20.87)	0.007[b]
Symptom onset suddenly, No. (%)	51 (89.47)	262 (66.67)	<0.001[b]
Language impairment, No. (%)	37 (64.91)	191 (48.60)	0.021[b]
Unilateral facial numbness or weakness, No. (%)	23 (40.35)	99 (25.19)	0.016[b]
Bilateral facial numbness or weakness, No. (%)	3 (5.26)	67 (17.04)	0.022[b]
Left arm weakness or numbness, No. (%)	27 (47.37)	131 (33.33)	0.038[b]
Unconsciousness or fainting, No. (%)	3 (5.26)	2 (0.01)	0.016[b]
Dizziness, loss of balance, difficulty walking, or loss of coordination, No. (%)	21 (36.84)	203 (51.65)	0.037[b]
Considered any of the symptoms to be severe, No. (%)	46 (80.70)	150 (12.72)	<0.001[b]
Recognized the problem as stroke, No. (%)	36 (63.16)	115 (29.26)	<0.001[b]
Bystanders' reactions suggested going to a hospital, No. (%)	56 (98.24)	272 (69.21)	<0.001[b]
Referred from other hospitals, No. (%)	6 (10.53)	127 (32.32)	0.020[b]
Used an ambulance for this occurrence, No. (%)	13 (22.80)	18 (4.58)	<0.001[b]
Symptom change before admission, No. (%)			
No change	27 (47.37)	102 (25.95)	<0.001[b]
Exacerbated	12 (21.05)	166 (42.24)	
Lightened	12 (21.05)	15 (3.82)	
Fluctuated	6 (10.53)	110 (27.99)	
Bystanders recognized the problem as stroke, No. (%)			
Yes	39 (68.42)	130 (33.08)	<0.001[b]
No	9 (15.79)	137 (34.86)	
Unknown	9 (15.79)	126 (32.06)	
Patient's response when symptoms first appeared, No. (%)			
Contacted relative/acquaintance	27 (47.37)	96 (24.43)	<0.001[b]
Called a physician	1 (1.75)	1 (0.00)	
Went directly to a hospital	17 (29.82)	54 (13.74)	
Self-administered medicine	2 (3.50)	65 (16.54)	
Called for emergency assistance	6 (10.53)	3 (0.01)	
Did nothing	4 (7.01)	174 (44.27)	
Knowledge about the time window for intravenous thrombolysis for stroke, No. (%)			
≤3 h	13 (22.80)	19 (4.83)	<0.001[b]
≤4.5 h	7 (12.28)	10 (2.54)	
≤6 h	14 (24.56)	46 (11.70)	
Unknown	23 (40.35)	318 (80.91)	
Monthly household income per capita (yuan), No. (%)			
<1,000	4 (7.01)	47 (11.96)	0.005[b]
1,000–2,999	22 (38.60)	204 (51.90)	
3,000–5,000	14 (24.56)	92 (23.41)	

(Continued)

TABLE 2 (Continued)

Factors	Prehospital delay time <3 h ($n = 57$)	Prehospital delay time ≥3 h ($n = 393$)	P-value[a]
>5,000	17 (29.82)	50 (12.72)	
Onset location, No. (%)			
Home	36 (63.16)	270 (68.70)	<0.001[b]
Workplace	4 (7.01)	66 (16.79)	
Public place	9 (15.79)	45 (11.45)	
In the car	6 (10.53)	4 (1.01)	
Other	2 (3.51)	8 (2.04)	
Distance between the place of onset and the investigating hospital, No. (%)			
≤5 km	8 (14.04)	12 (3.05)	<0.001[b]
>5 and ≤10 km	9 (15.79)	32 (8.14)	
>10 and ≤20 km	17 (29.82)	50 (12.72)	
>20 km	23 (40.35)	299 (76.08)	
Transportation to the first hospital, No. (%)			
Car	33 (57.89)	268 (68.19)	<0.001[b]
Ambulance	10 (17.54)	14 (3.56)	
Other	14 (24.56)	111 (28.24)	
Ischemic stroke type, No. (%)			
Anterior circulation stroke	38 (66.67)	147 (37.40)	<0.001[b]
Posterior circulation stroke	19 (33.33)	217 (55.22)	
Unknown	0 (0.00)	49 (12.47)	
Stroke aura symptom awareness, mean (SD)[d]	7.18 (2.00)	6.58 (2.35)	0.043[c]

[a]Only statistically significant variables are included.
[b]Chi-square test.
[c]t-test.
[d]Stroke aura symptoms awareness questionnaire-9 is a test for stroke aura symptoms awareness.

Their major areas of expertise were emergency medicine (1/18) and neurology (17/18). During the two rounds of Delphi consultation, 18 questionnaires were issued and recovered, with a 100% recovery rate.

Data analysis

SPSS software was used for data entry and computation. Missing values were also obtained using the maximum likelihood method in SPSS. Responses to the survey questions were analyzed using descriptive statistics (significance was set at $P < 0.05$). Using the prehospital delay time (3 h) as a cut-off point, patients were divided into two groups: the timely admission group (≤3 h) and the delayed admission group (>3 h). Qualitative variables were expressed as numbers (percentages). The chi-square test was used for comparisons. Continuous normally distributed variables were expressed as mean ± standard deviation and compared using Student's t-test.

Risk level assessment method

A risk matrix was constructed based on the identified risk factors for prehospital delay combined with expert opinions. The Borda count is designed to rank different risk factors according to their importance. The risk matrix is a structured approach used to identify the importance of risk during project management. It assesses the potential impact of risk through a simple operational method and qualitative and quantitative analyses. The traditional risk matrix level is determined by the combination of the probability of occurrence of the risk and the severity of the consequences. Risk grading according to the corresponding values was presented in Table 1.

The Borda count method is a well-known social choice method that is frequently used for group decision-making problems (25). This method can determine the winner of an election by giving each candidate a certain number of points corresponding to the position at which each voter ranks them. Risk factors are sorted based on the significance of the following criteria that reduce the subjectivity of experts. k is the different risk assessment criteria ($k1$, $k2$, and $k3$ represent the risk impact, risk probability, and risk level, respectively). N is the total

TABLE 3 Prehospital delay risk matrix for stroke.

No.	Risk factors	Risk impact degree	Quantitative value of the degree of risk impact	Possibility of risk occurrence	Quantitative value of the probability of risk occurrence	Risk rank	Borda number	Borda count
A1	Living in a rural area	Critical	4.11	Very likely	4.17	V	84	0
A2	Low family income	Severe	3.67	More likely	3.83	IV	61	9
A3	No health insurance or low reimbursement	Severe	3.56	More likely	3.72	IV	61	9
A4	Physical examination less than once per year	Severe	3.11	More likely	3.22	IV	61	9
A5	Posterior circulation stroke	Severe	3.22	More likely	3.22	IV	61	9
A6	Minor symptoms (NIHSS[a] score <4)	Severe	3.22	More likely	3.33	IV	61	9
A7	Bilateral face cavity/mouse skew	General	2.83	Likely	2.78	III	6	26
A8	Limb weakness and numbness	Severe	3.28	More likely	3.06	IV	61	9
A9	Dizziness/unsteadiness of gait	General	2.94	Likely	3.00	III	6	26
A10	Wake-up stroke	Severe	3.50	More likely	3.33	IV	61	9
A11	Gradual progression of symptoms	Severe	3.94	More likely	3.94	IV	61	9
A12	Symptoms were alleviated prior to admission	Severe	3.50	More likely	3.56	IV	61	9
A13	No bystanders when stroke occurred	Critical	4.44	Very likely	4.06	V	84	0
A14	After stroke onset, bystanders failed to recognize the stroke	Severe	3.56	More likely	3.61	IV	61	9
A15	Patients and their families have low awareness of premonitory symptoms of stroke	Severe	3.50	More likely	3.44	IV	61	9
A16	Patients and their family members have a low level of stroke knowledge	Critical	4.17	More likely	3.94	V	79	5
A17	Attributed the symptoms of other diseases after onset	Severe	3.94	More likely	3.83	IV	61	9
A18	Patients and their families lack an understanding of the urgency of stroke treatment	Critical	4.39	Very likely	4.28	V	84	0
A19	Patients and their families do not know that stroke requires thrombolysis and that there is a thrombolysis time window	Critical	4.61	Very likely	4.33	V	84	0
A20	Patient self-medicates, does not think that the symptoms are serious, and waits for spontaneous remission	Critical	4.17	Very likely	4.11	V	84	0
B1	Patient chooses other means of transportation instead of EMS[b]	Severe	3.11	More likely	3.33	IV	61	9
B2	Onset location is distant from the general hospital	Critical	4.22	More likely	3.89	V	79	5
B3	Emergency workers lack knowledge of stroke	Severe	3.67	More likely	3.33	IV	61	9
B4	Paramedics did not contact the hospital in advance	Severe	3.61	More likely	3.39	IV	61	9
B5	Lack of first aid resources (such as insufficient ambulances, uneven medical resource distribution, blocked first aid channels, etc.)	Critical	4.11	More likely	3.78	V	79	5
B6	The hospital where the patient is treated during the first stroke is a primary medical institution and there are no corresponding treatment and thrombolysis conditions	Critical	4.22	More likely	3.83	V	79	5
B7	Traffic	Severe	3.72	More likely	3.56	IV	61	9
B8	Outside hospital transfer	Severe	3.67	More likely	3.39	IV	61	9

[a]NIHSS, National Institutes of Health Stroke Scale. [b]EMS, emergency medical services.

number of risks; i is the total number of risks for risk i ($1 \leq i \leq N$); R_{ik} represents the k criterion, which is the risk level of the number i ranked, that is, the number of risks that are more severe than risk i among the total risks of N. The Borda number determines the Borda count. A Borda count of 0 indicates the most critical risk. The Borda number of risks i can be obtained by the following formula:

$$b_i = \sum_{k=1} (N - R_{ik}) \qquad (1)$$

The risk level is determined by the probability of risk occurrence and the severity of the consequences. During this study, the risk grade was divided into five levels: I, II, III, IV, and V. Scores ranged from I to V, with higher scores indicating higher risk rating.

Results

Determination of 28 risk evaluation metrics

A total of 450 patients admitted to the neurology ward were recruited and enrolled in the study. Only 12.7% of the patients arrived at the hospital within 3 h, and 32.4% of the patients had never known about or heard of stroke. Significant factors in the univariate analysis ($P < 0.05$) were applied in the risk indicator system for prehospital delay (Table 2). Twenty-eight specific risk indicators were identified, including patient delay and transport delay risk (Table 3).

Delphi expert consultation

Expert authority coefficient

According to the expert self-evaluation scores, the authoritative coefficients of various indicators reached more than 0.80 for the 18 experts. The coefficient of authority was 0.95. It was demonstrated that the participating experts had a high level of familiarity with the indexes, including research and work experience in these areas. Therefore, the selection of indices and results had high credibility.

Degree of expert coordination

The Kendall coordination coefficient (W) refers to whether there are significant differences between the opinions of the experts evaluating each index. W ranges between 0 and 1, with a greater value indicating a higher degree of concordance between the experts. During this study, the expert coordination coefficient (W) was 0.254 ($P < 0.001$), which suggested that the concordance of the expert opinions was high.
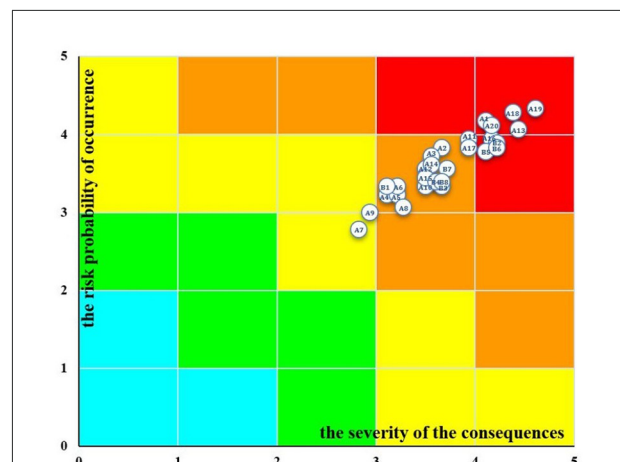

FIGURE 1
Prehospital delay risk matrix map of stroke. There are five colors in the risk matrix diagram that represent different degrees of risk and corresponding processing methods. Blue corresponds to very low risk (I), green corresponds to low risk (II), yellow corresponds to medium risk (III), orange corresponds to high risk (IV), and red corresponds to very high risk (V).

Determination of risk rating

The probability of risk occurrence and the severity of consequences were used to determine the risk rating. The expert scoring methods designated the probability of risk occurrence and the severity of the consequences. All expert opinions and the mean are summarized in Table 3. The risk matrix diagram was drawn using the severity of the consequences as the abscissa and the probability of risk occurrence as the ordinate (Figure 1). The Borda scores were presented in Table 3. There were five risk factors with a Borda count of 0: living in a rural area (A1); no bystanders when stroke occurred (A13); patients and their families lacking understanding about the urgency of stroke treatment (A18); patients and their families not knowing that stroke requires thrombolysis or about the thrombolysis time window (A19); and the patient self-medicating, not thinking that the symptoms are serious, and waiting for spontaneous remission (A20). These five risk factors were the most critical for prehospital delay after stroke.

Discussion

During the current study, 32.4% of the patients had never heard of stroke. Among patients who had heard of the disease, the single rate of awareness of common stroke symptoms and risk factors were relatively high. However, the overall awareness rates were lower compared to other studies. For example, Nordanstig et al. (26) and Sundseth et al. (27) reported rates of 50.0% and 39.5%, respectively. Our study indicated that patients

have insufficient knowledge of stroke symptoms and risk factors, and their understanding of stroke prevention and treatment needs to be improved (A18, A19, and A20). Similar to previous studies (11, 28), the present study showed that prehospital delay is caused by inadequate acknowledgment of the seriousness of disease, which leads to a lack of urgency to change behaviors. Rural residence was determined as one of the critical factors for prehospital delay, which may be associated with insufficient medical resources. The survey results were consistent with the investigation results because patients with prehospital delay inhabited economically underdeveloped and geographically remote areas, and their medical and health resources were relatively scarce. Additionally, the lack of help from others at the time of stroke onset was a key factor in prehospital delay. Ischemic stroke is a heterogeneous disorder characterized by a variety of clinical symptoms. Hence, bystander awareness and intervention are essential. When a patient presents with fainting and limb stiffness or similar and/or more severe symptoms, bystanders will take immediate action. If the patient experiences mild symptoms (dizziness, numb limbs, etc.), then the delay time depends on the recognition of the severity of those symptoms. When the patients or bystanders realize something is abnormal, they should seek medical help immediately. On the contrary, if there are no bystanders, then the condition may deteriorate unless the patients are able to promptly recognize the symptoms themselves.

The results of this study can be used to develop new clinical assessment tools for the healthcare data domain. These tools may contribute to prioritizing interventions for the at-risk population and have a certain practical value. Additionally, this study creatively constructed the risk matrix and identified the key risk factors for prehospital delay with stroke, which can provide a basis for the implementation of comprehensive and effective interventions and risk prevention measures and a theoretical basis for proposing and developing management strategies.

When the five most practical factors are identified by the Borda count and risk matrix, adaptation recommendations for interventions may be proposed accordingly. Regarding the high-risk factor of living in rural areas (A1), the cost of living in rural areas may be lower, but patients in these areas are typically older and have less access to transportation. They also have lower educational levels, poorer housing conditions, higher poverty rates, poorer health, and more disabilities than their urban counterparts. In underserved rural communities, nurses are often frontline healthcare professionals. Some researchers believed that healthcare professionals implement information technology to achieve interdisciplinary medical cooperation in rural areas, which can effectively improve care; therefore, the informatics knowledge and skills of the nursing staff in rural areas must be upgraded (29). Some researchers have pointed out that telemedicine has been mainly used to access certain health services for populations living in remote areas (30). Furthermore, many researchers have pointed out that the

implementation of stroke telemedicine can help increase the rate of intravenous thrombolysis, confirming that the application of stroke telemedicine to cerebrovascular diseases has excellent potential (31, 32). Therefore, strengthening the advancement of stroke telemedicine care can improve, to a certain extent, the imbalanced allocation of medical resources for stroke and the lack of senior medical personnel in remote areas.

Because one risk factor is the absence of bystanders when stroke occurs (A13), community workers should provide better care for elderly individuals living alone. Interacting with elderly people living alone through community activities, identifying their illnesses, and promptly providing appropriate care are important during the early management of stroke patients. This can be offered as part of a holistic and individualized care plan by the professional community nurse.

We attributed the following three risk factors to the lack of knowledge about stroke: A18, A19, and A20. To reduce prehospital delay for stroke patients, hospitals and community health service centers should collaborate to improve the knowledge of the general public regarding the urgency of stroke treatment, the need for thrombolysis, the thrombolysis time window, common stroke symptoms, and how to recognize the severity of stroke-related symptoms to decrease mortality and disability rates of stroke patients, especially those in rural areas. Community nurses have been patient advocates, patient educators, and case managers for quite some time. Therefore, the expertise that nurses can contribute to improving the health of underserved rural communities *via* information technology methods is considerable (29). Mass media is a powerful way of disseminating information about the health effects of prehospital delay to the general public; therefore, efforts should be made to take advantage of mass media to extend the reach of informational messages regarding stroke (28). For example, a wide range of health education activities can be regularly performed for community residents through the internet, radio, television, newspapers, publicity boards, brochures, and lectures.

This is the first study to use the risk matrix and Borda count to identify high-risk factors for prehospital delay among stroke patients. However, this study had some limitations. First, convenience samples may be biased because individuals who choose to participate in the study may not fully represent the population from which the sample has been drawn. Second, because of the cross-sectional design of the study, causality could not be inferred. Therefore, longitudinal studies are required to infer actual causal relationships.

Conclusions

This study established a risk assessment tool to evaluate the prehospital delay risk for stroke patients using the risk matrix and Borda count. In this risk assessment framework, five significant risk factors were identified and could be used to evaluate the risk factors for prehospital delay based on

the probability of risk occurrence and the severity of the consequences. This practical and objective tool can guide risk management and reduce prehospital delay activities as an essential public health strategy. It is anticipated that this prehospital delay risk assessment tool will be further developed and find further applications and will be adapted based on cultural differences. By establishing a risk assessment tool, we can continually evaluate and refine risk factors, focus on key risk factors, and perform targeted preventive measures.

Data availability statement

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

Ethics statement

This study was approved by the Research Ethics Committee of Harbin Medical University, Harbin, China (Ref. No. KY2017-063). The study purpose statement was read by all study subjects and each provided written informed consent. The patients' identity information was kept confidential. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZG and QL were responsible for the study conception, design, and drafting of the manuscript. ZG, LY, QL, and XZ

collated data and conducted data analyses. LY was responsible for supervision. All authors made critical revisions to the manuscript.

Conflict of interest

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

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Frontiers in Public Health

Role of rumination and hope on negative life events and suicidal ideation under the background of normalization of pandemic prevention and control: A moderated mediation model

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Introduction: The study aimed to investigate the impact and mechanism of negative life events on college students' suicidal ideation during the COVID-19 pandemic and the buffering effect of hope under the background of normalization of pandemic.

Methods: A total of 5211 participants took part in this study. Self-reported negative life events, rumination, hope and suicide ideation were measured using a range of questions and scales. Our research demonstrated that the incidence of suicidal ideation among college freshmen in the past week was higher during the COVID-19 pandemic than that before the pandemic. In this study, conditional process model 15 was used to verify the hypothetical model of rumination as a potential mediator and hope as a moderator.

Results: The hypothesized moderated mediation model was verified significant (β = -0.047, 95% CI = [-0.061, -0.035]), and hope was found to moderate the direct effect of negative life events on suicidal ideation (β = -0.039, t = -2.937, 95% CI = [-0.065, -0.013]) as well as the indirect effect of through the mediator rumination (β = -0.134, t = -10.850, 95% CI = [-0.158, -0.110]).

Discussion: We found that rumination partially mediated the effect of negative life events on suicidal ideation, and hope buffered the direct and indirect effect of negative life events on suicidal ideation. The implications of the findings for clinical interventions are discussed, including the importance of hope arousal as a protective factor and rumination as a cognitive mechanism for emotion regulation under the background of normalization of pandemic.

KEYWORDS

negative life events, rumination, hope, COVID-19, suicidal ideation

1. Introduction

The outbreak of COVID-19, which infected more than 643 million people as of December 2022, had a significant impact across the entire world. As a result, public health departments of governments and other health authorities across the globe have undertaken a wide range of interventions, including nationwide lockdowns, home quarantining, and social distancing, to slow and control the spread of COVID-19. Regarding the impact of COVID-19 and subsequent

quarantine on an individual's health, depression and suicidal ideation were seen as the most serious factors, as they have been identified as the factors most strongly associated with suicide (1, 2). College students, in particular, have been considered a vulnerable group who have been found to experience more mental health problems (e.g., depressive symptoms and suicidal ideation) than other adults (3), with neuroticism and stressful experiences as the main factors influencing the increase of suicidal ideation in college students (4). Furthermore, negative life events are considered to be an important indicator of suicidal ideation (5, 6). After the outbreak of the COVID-19 pandemic, college students were faced with stricter campus management, along with the possibility of an increase in negative life events, which further brought severe challenges to college students.

In April 2021, the State Council Information Office of China proposed that the country has entered the normalization stage of epidemic prevention and control (7), with significantly reduced cases of infectious diseases, effective treatment of sporadic infectious diseases, and normal operation of the public health management system. Nevertheless, the impact of COVID-19 continues, and the threat has not been eliminated. Nowadays, the harm of COVID-19 to people's physical health is gradually diminishing, but the impact on people's lives and mental health is ongoing (8, 9). Preventing and eliminating the psychological panic caused by a pandemic is a key issue facing the world today. Under the background of normalized pandemic prevention and control, what is the status of suicidal ideation among college students in the continuous adjustment of the government's prevention and control policy environment? How should suicide crisis intervention be carried out in college and university settings under the background of normalization? In attempting to address these core issues, this study aims to (1) explore the status of suicidal ideation among college students under the background of normalization and (2) discover the influence mechanism of negative life events on suicidal ideation, in order to better advise school counselors and mental health center staffs on early intervention for high-risk populations.

1.1. Negative life events, rumination, and suicidal ideation

The stress-diathesis model, proposed by Mann et al. (10), believes that the suicidal risk of an individual is the result of the interaction between an individual's diathesis and the negative life events, including acute mental illness or physical disease, work pressure, adverse interpersonal relationship, severe trauma, and so on. Quite a few suicide theories (10–12) include environmental factors as important antecedent variables of suicidal ideation. Previous studies found that negative life events are important antecedents of depression, despair, suicidal ideation, and even suicidal behavior (13–16). Based on the theories and previous studies, we hypothesized that the combination of physical and mental stress caused by the pandemic (such as worrying about the risk of infection of oneself or the surrounding relatives) and other stressful events may exacerbate suicidal ideation in students.

The integrated motivational-volitional (IMV) model of suicidal behavior (11, 17) proposed that suicide develops in three phases and conducted a detailed theoretical discussion on the relationship between negative life events, rumination, and suicidal ideation. The

first phase is the pre-motivational phase, which focuses on distal factors and triggers of suicide risk, including diathesis, environment, and life events. The second phase is the motivational phase, which describes the psychological processes that induce suicidal thoughts and intentions that derive from entrapment triggered by feelings of defeat and humiliation. Self-threatening factors, such as rumination, affect entrapment, as well as the relationship between defeat and entrapment. Rumination is generally considered a maladaptive cognitive process in which an individual repeatedly attempts to analyze problems and painful feelings without taking the necessary action to make positive changes (18, 19).

A growing number of empirical studies also demonstrated that rumination could mediate the impact of negative life events on suicidal ideation (20, 21). Wenzel et al. pointed out that constant immersion in perceptions and influences associated with negative life events might cause individuals to consider suicide, eventually developing a suicidal plan as a solution to their problems (22). Rumination leads to a worsening emotional state, such as more anger and less happiness (23), and has a significant impact on individual mental health, including depressive symptoms (24). The maladaptive nature of rumination is particularly evident in individuals with major depressive episodes (19), and rumination is a risk factor for suicidal ideation (6) and suicide attempts (19, 25). In addition, rumination mediates the impacts of negative life events, childhood trauma, and loneliness on suicidal ideation (6, 26) and even suicidal behaviors (21). Therefore, we hypothesize that negative life events are positively associated with suicidal ideation, and rumination mediates the impact of negative life events on suicidal ideation (Hypothesis 1).

1.2. The moderating role of hope on the relationship between negative life events and suicidal ideation

When considering suicidal ideation, some positive psychological structures, such as hope, may be particularly important as protective factors (27). Hope is an individual's mental resilience in the face of future goals (28). Two sub-components of hope comprise the perception of the ability to determine feasible paths to a destination (i.e., pathways thinking) and the perception of being able to use those routes to successfully reach a goal (i.e., agency thinking). Hope, associated with specific goals, can support people to get through persistent negative emotions and, in turn, find meanings out of their sufferings, which has been reported to have protective effects on one's mental health (29). The moderating effect of hope on suicidal ideation has been extensively demonstrated (30–33). Hope moderates the effects of traumatic events on suicidal ideation (30, 32) and alleviates the influence of antecedent factors on suicidal ideation by improving individual coping ability (32). Individuals with a higher level of hope have better-coping strategies (34) and less suicidal ideation (35). Hope theory believes that individuals with high levels of hope will achieve better in various domains, including more positive emotions (28). Hope can also moderate the effect of negative life events on depressive symptoms, one of the most risk elements for suicidal ideation (36). It has been found that improvement of both pathways thinking and agency thinking is beneficial to mental health status (37), and the promotion of hope will be the basic method of adolescent crisis intervention (38). Therefore, based on the

FIGURE 1
Theoretical hypothesis model-moderated mediation model.
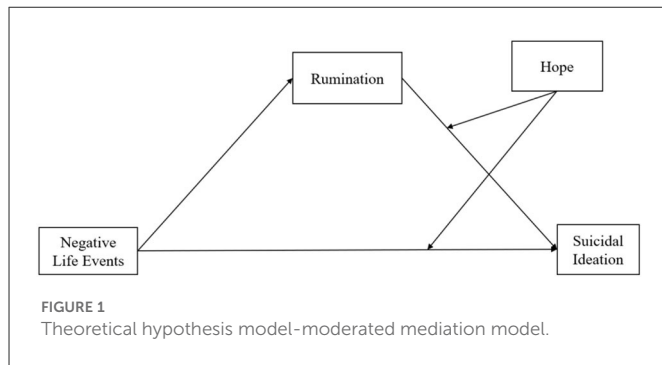
hope theory and the buffering hypothesis, it is proposed that hope can moderate the effect of negative life events on suicidal ideation (Hypothesis 2).

1.3. The moderating role of hope on the relationship between rumination and suicidal ideation

The IMV model also proposes that motivational variables play moderating roles in the development of depression to suicidal ideation and suicidal intention. Hope, considered one of the motivational factors, can moderate the influence of individual distress on suicidal ideation (33) theoretically. When a goal is blocked, individuals with higher hope are more flexible in seeking and finding alternative paths, which is a powerful mitigating factor for rumination (33, 39). Evoking hope has been found to ameliorate rumination (23). Studies also found that hope moderated the influence of rumination on depressive symptoms in Chinese college students (40). Specifically, rumination significantly predicated depressive symptoms in students with lower hope, but not among students with high hopes (40). Therefore, hope is hypothesized to moderate the effect of rumination on suicide risk (Hypothesis 3).

1.4. Present study

The toll of the COVID-19 pandemic on suicidal ideation has been wildly studied, but it is limited in exploring the function of positive psychological structures during the pandemic. There is no specific exploration of suicidal ideation under the context of the normalization of pandemic prevention and control. To bridge the gap, our study examined the association between negative life events and suicidal ideation under the normalization circumstance in Chinese college students and tested the role of rumination as a mediator and hope as a moderator.

We propose a moderated mediation model as presented in Figure 1 with three hypotheses. First, it is hypothesized that negative life events are positively correlated with suicidal ideation and that rumination plays a mediating role between them. The second hypothesis is that hope moderates the influence of negative life events on suicidal ideation. The third and final hypothesis is that hope buffers the relationship between rumination and suicidal ideation.

2. Materials and methods

2.1. Participants and sampling

We conducted an online survey of Chinese college students from three universities in Fujian Province during the COVID-19 pandemic using a cross-sectional approach. A mixture of convenience sampling and snowball sampling was used for data collection. A total of 5,632 college students participated in this study, 239 participants did not complete the questionnaire and were excluded, and 182 students were diagnosed with mental disorders and were also excluded, yielding an inclusion rate of 92.52%.

The final sample consisted of 5,211 participants, of whom 55.1% were female. The age ranged from 15 to 38 years ($M_{age} = 20.74$, $SD = 2.99$). There were 2,590 (49.7%) students who majored in natural science, 1,996 (38.3%) students who majored in humanities and social sciences, and 625 (12.0%) students who majored in arts.

Prior to the investigation, participants were notified through the Wechat App about the purpose and procedure of our study. Written consent was obtained online from all participants before accessing the questionnaire.

2.2. Measures

2.2.1. The adolescent self-rating life events checklist

Negative life events were measured by ASLEC, containing 27 statements about various life events (e.g., "Relatives and friends suffer from acute or serious illness" and "Being discriminated against") that may cause psychological distress in adolescents, using a 5-point (0 = no impact, 5 = always impact) Likert scale, and the Chinese version was validated in 1997 (41). A total life stress score was calculated by adding scores on all the items together. The higher the total score, the greater the amount of stress from negative life events. The internal consistency coefficient in the study was 0.947.

2.2.2. Ruminative Responses Scale

Rumination was measured by the Ruminative Responses Scale (42), which consists of 22 items that assess individual responses to depressed mood. Participants reported the frequency of engaging in various ruminative thoughts and behaviors on a 4-point (1 = almost never, 4 = almost always) Likert-type scale (e.g., "I often wonder why I can't get started"). The total score was calculated as the sum of all items with higher scores indicating a greater tendency to ruminate. The internal consistency of RRS in this study was good (Cronbach's $\alpha = 0.943$).

2.2.3. Adult Dispositional Hope Scale

Hope was assessed using the 12-item Adult Dispositional Hope Scale (43). The Chinese version was validated in 2009 (44). The ADHS is composed of two subscales, namely, pathways thinking and agency thinking. Each subscale consists of four items; for example, the items include "There are always many ways to solve any problem" for pathways thinking and "My experience has prepared me well for my future" for agency thinking. Participants were asked to rate

TABLE 1 Demographic characteristics of the study sample.

Gender	Suicidal ideation	Education level	Suicidal ideation	Major	Suicidal ideation
Male (N = 2,309)	0.34 ± 0.98	Undergraduate (N = 2,571)	0.47 ± 1.18	Natural science (N = 2,590)	0.28 ± 0.86
Female (N = 2,837)	0.36 ± 1.02	Graduate (N = 2,607)	0.23 ± 0.77	Humanities and social sciences (N = 1,996)	0.36 ± 1.00
				Art category (N = 625)	0.66 ± 1.42
t	−0.728	t	8.58	F	36.569
p	0.466	p	0.000	p	0.000

how accurately each item described them on a seven-point Likert-type scale from 1 (absolutely false) to 7 (absolutely true). Higher scores correspond to higher levels of hope. In this sample, ADHS demonstrated good internal consistency (Cronbach's $\alpha = 0.872$).

2.2.4. Beck scale for suicide ideation

A total of 5 questions were asked to measure the suicidal ideation in the last week from five items rated on a 3-point scale (ranging from 0 to 2): willingness to live, willingness to die, the reasons for survival or death, active suicidal ideation, and the passive suicidal ideation. Higher scores are indicative of stronger suicidal ideation. The internal consistency coefficient of the scale was 0.792.

2.3. Data analysis

Correlation analysis was used to check for the bivariate associations between variables. Spearman's correlations were used to analyze non-normal distributions of continuous variables. Descriptive statistics on demographic characteristics and related variables were initially reported. Participants with and without suicidal ideation were compared.

We used the PROCESS Model 15 to test a moderated mediation model with bootstrap confidence intervals for conditional effects. Moreover, a bias-corrected bootstrap procedure was used to generate 95% bias-corrected confidence intervals (CI) from 5,000 samples to test the significance of moderating mediating effects. SPSS 20.0 version was used for the above analyses. The two-tailed significance level was set at $p < 0.05$.

3. Results

The items included in all the measures mentioned above were analyzed by exploratory factors, and common method biases were tested using Harman's univariate analysis (45). There were 21 factors with eigenvalues >1. They account for an acceptable percentage (26.34%) of total variation compared to the criterion of 40%, which means no obvious common method bias in our study.

3.1. Descriptive statistics and correlations

Table 1 shows the demographic characteristics of the study sample. There was no significant difference in suicidal ideation scores

TABLE 2 T-test of concerned variables between the groups with and without suicidal ideation.

Variables	Suicidal ideation group	No suicidal ideation group	t
	(N = 501)	(N = 4,710)	
	M ± SD	M ± SD	
Negative life events	54.36 ± 20.71	44.08 ± 17.13	10.72***
Rumination	2.43 ± 0.62	1.91 ± 0.53	18.49***
Hope	2.47 ± 0.47	2.91 ± 0.50	−19.21***

***$p < 0.001$.

between male and female students ($t = -0.728$, $p = 0.466$), as shown in Table 1. There was a statistically significant difference in the educational level of subjects on suicidal ideation ($t = 8.58$, $p < 0.001$), with the suicidal ideation rate of undergraduates being significantly higher than that of graduates. The differences across majors were statistically significant on suicidal ideation ($F = 36.569$, $p < 0.001$), with the arts students being significantly higher than the other two groupings, and the scores of humanities and social science students were significantly higher than the science and engineering students.

Table 2 shows the t-test results of suicidal ideation in two groups. Students were divided into groups with or without suicidal ideation based on two questions from the BSS-5 ("active suicidal ideation" and "passive suicidal ideation") as grouping criteria. To be specific, students who said "no" to both two questions were assigned to the group without suicidal ideation; otherwise, they were assigned to another group. The results showed that 501 students had suicidal ideation in the last week, accounting for 9.61% of all the participants. The t-test results indicated that the scores of negative life events and rumination in the group with suicidal ideation were significantly higher than those in the group without suicidal ideation (t scores were 10.72 and 18.49, respectively, $p < 0.001$), and the scores of hope were significantly lower in the group with suicidal ideation ($t = -19.21$, $p < 0.001$).

Table 3 represents the descriptive statistics and correlation coefficients among all the variables. Suicidal ideation had a significant positive correlation with negative life event scores ($r = 0.21$, $p < 0.001$) and rumination scores ($r = 0.24$, $p < 0.001$) and had a significant negative correlation with hope scores ($r = -0.26$, $p < 0.001$). Negative life events had a positive correlation with rumination ($r = 0.43$, $p < 0.001$).

TABLE 3　Descriptive statistics and correlations between variables.

	$M \pm SD$	Gender	Age	Negative life events	Rumination	Hope	Suicidal ideation
Gender	–	1					
Age	20.74 ± 2.99	-0.068^{**}	1				
Negative life events	45.08 ± 17.77	$0.032*$	-0.126^{**}	1			
Rumination	1.96 ± 0.56	0.059^{**}	-0.199^{**}	0.43^{***}	1		
Hope	2.87 ± 0.52	-0.072^{**}	0.180^{**}	-0.29^{***}	-0.30^{***}	1	
Suicidal ideation	0.35 ± 1.01	0.020	-0.124^{**}	0.21^{***}	0.24^{***}	-0.26^{***}	1

$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

We used path analysis to test the direct effect of negative life events on suicidal ideation and the moderating effect of hope on the direct path. After controlling gender and age as covariates, negative life events were found to have a significant effect on suicidal ideation [$\beta = 0.127$, $t = 9.777$, 95% CI $= (0.101, 0.152)$]. Hope negatively predicted suicidal ideation [$\beta = -0.207$, $t = -15.932$, 95% CI $= (-0.233, -0.182)$]. Hope also significantly moderated the effect of negative life events on suicidal ideation [$\beta = -0.097$, $t = -7.771$, 95% CI $= (-0.121, -0.073)$].

3.2. Rumination mediated the association between negative life events and suicidal ideation (Hypothesis 1)

To test Hypothesis 1, we used Process Model 4 in PROCESS procedures (46) to detect the mediation model that negative life events influence suicidal ideation through rumination. As shown in Table 4, the path analysis indicated that the direct effect of negative life events on suicidal ideation was significant [$\beta = 0.127$, $t = 9.777$, $p < 0.001$, 95% CI $= (0.101, 0.152)$]. The indirect effect through rumination was significant [$\beta = 0.202$, $t = 14.485$, $p < 0.001$, 95% CI $= (0.175, 0.229)$]. The mediating effect path is shown in Table 4. After adding the mediating variable, the influence coefficient of negative life events on suicidal ideation decreased, and the 95% CI of the mediating effect size [95% CI $= (0.057, 0.086)$] through rumination did not contain 0, which means rumination partially mediated the association between negative life events and suicidal ideation. The mediating effect accounted for 39.89% of the total effect. The model explained 8.5% of the variation in suicidal ideation. Therefore, Hypothesis 1 was supported.

3.3. Hope as a moderator (Hypotheses 2 and 3)

To test Hypothesis 2 and 3, we established a moderated mediation model using Model 15 to determine whether the effect of negative life events on suicidal ideation was moderated by hope. The results presented in Table 5 demonstrated that negative life events had a significant positive predictive effect on suicidal ideation [$\beta = 0.077$, $t = 5.781$, 95% CI $= (0.051, 0.103)$]. Rumination had a significant positive predictive effect on suicidal ideation [$\beta = 0.163$, $t = 11.890$,

95% CI $= (0.136, 0.190)$]. The interaction between negative life events and hope had a significant predictive effect on suicidal ideation [$\beta = -0.039$, $t = -2.937$, 95% CI $= (-0.065, -0.013)$]. The interaction between rumination and hope had a significant predictive effect on suicidal ideation [$\beta = -0.134$, $t = -10.850$, 95% CI $= (-0.158, -0.110)$]. The results supported Hypothesis 2 and 3. The moderated mediation model was verified significant [$\beta = -0.047$, 95% CI $= (-0.061, -0.035)$], and hope was found to moderate the direct effect of negative life events on suicidal ideation as well as the indirect effect through the mediator rumination. The model explained 14.5% of the variation in suicidal ideation.

The predictive effect of negative life events on suicidal ideation at different levels of hope (1 SD above or below the mean) was further examined by simple slopes analysis. The results showed that the positive predictive effect of negative life events on suicidal ideation was significant at a low level (1 SD below the mean) of hope [$\beta_{simple} = 0.116$, $t = 6.529$, $p < 0.001$, 95% CI $= (0.081, 0.150)$], and at a high level (1 SD above the mean) of trait hope, negative life events had no significant predictive effect on suicidal ideation [$\beta_{simple} = 0.038$, $t = 1.907$, $p = 0.057$, 95% CI $= (-0.001, 0.077)$], which indicates that a higher sense of hope could mitigate the effects of negative life events on suicidal ideation. A simple effect slope diagram is shown in Figure 2.

According to the findings of simple slopes analysis, we further examined the predictive effect of rumination on suicidal ideation at different levels of hope (1 SD above and below the mean). The results showed that rumination had a significant positive predictive effect on suicidal ideation at low levels of hope [$\beta_{simple} = 0.295$, $t = 16.286$, $p < 0.001$, 95% CI $= (0.260, 0.331)$], but at high levels of hope, rumination had no significant predictive effect on suicidal ideation [$\beta_{simple} = 0.029$, $t = 1.523$, $p = 0.128$, 95% CI $= (-0.008, 0.065)$]. The additional results of the slopes analysis (Figure 3) indicated that the slope of the indirect effect was greater for a lower level of hope than for a higher level of hope, which means that hope could mitigate the effects of rumination on suicidal ideation.

In addition, hope was found to moderate the indirect effect of negative life events on the prediction of suicidal ideation through rumination, and the moderated mediating effect size was -0.047 with 95% CI $(-0.061, -0.034)$. At a low level of hope (1 SD below the mean), the indirect effect of negative life events on suicidal ideation through rumination was significant [$\beta = 0.104$, 95% CI $= (0.080, 0.128)$]. At a high level of hope (1 SD above the mean), the indirect effect of negative life events on suicidal

TABLE 4 Descriptive statistics and correlations between variables.

	Path	Effect	SE	95% CI	
				Lower	Upper
Direct effect	Negative life events-suicidal ideation	0.107	0.014	0.081	0.134
Mediating effect path	Negative life events -rumination -suicidal ideation	0.071	0.007	0.057	0.086
Total effect		0.178	0.013	0.153	0.204

ideation through rumination was not significant [$\beta = 0.010$, 95% CI = $(-0.001, 0.021)$].

4. Discussion

Our study focuses on the suicide ideation of college students under the context of normalization of pandemic prevention and control in China. It was a meaningful perspective and expansion on distinguishing the potential detailed difference between suicidal ideation during the outbreaking period of the pandemic and suicidal ideation during the normalization period of it. It verified the mediating role of rumination, which is consistent with the previous study during the outbreaking period of COVID-19 (6). Second, our study also explored the moderating effect of hope on negative life events and rumination. It enriches the research of hope theory under the background of the COVID-19 pandemic. It complemented the previous study in suicidology that did not pay enough attention to the positive psychological structure of individuals, especially during the pandemic, and it also promoted the exploration and enlightenment of the suicide prevention mechanism for college students from the perspective of hope.

4.1. The suicidal ideation of college students under the context of normalization of pandemic prevention and control

This study focuses on the suicidal ideation of college students under the context of normalization of pandemic prevention and control. In our studies, the prevalence of suicidal ideation among college students in the past week was 9.61%, which was much higher than the data reported on suicidal ideation (2.60–6.18%) (47). Another study showed that the prevalence of suicidal ideation rose from the early phase (7.6%) to the later phase (10.0%) during the COVID-19 pandemic. A cohort study of employees from Japan and a longitudinal study of adults in the United Kingdom also reported an increase in the incidence of suicidal ideation during the COVID-19 pandemic (48, 49). Perhaps due to long-time isolation and restrictions, college students feel confused and fearful about their future career or academic development, which causes a lot of mental health problems (50). In conclusion, these findings suggest that suicidal ideation has become an even more important and urgent public health problem due to the COVID-19 pandemic (49, 51).

Therefore, there is a need to improve suicide prevention strategies during this period of time. In the mitigation period of the pandemic, colleges and universities have exercised more stringent control over collective activities, thereby reducing collaborative opportunities, such as team building, class integration, and community activities. Limited interpersonal communication and occasional outbreaks may contribute to adjustment difficulties and emotional distress in college students. Given the characteristics of the pandemic remission period, colleges and universities need to make further adjustments in the provision of mental health services, such as popularizing mental health knowledge through the media, increasing awareness of and access to psychological help hotlines, and launching online psychological counseling services to meet the psychological needs of students in a timely fashion.
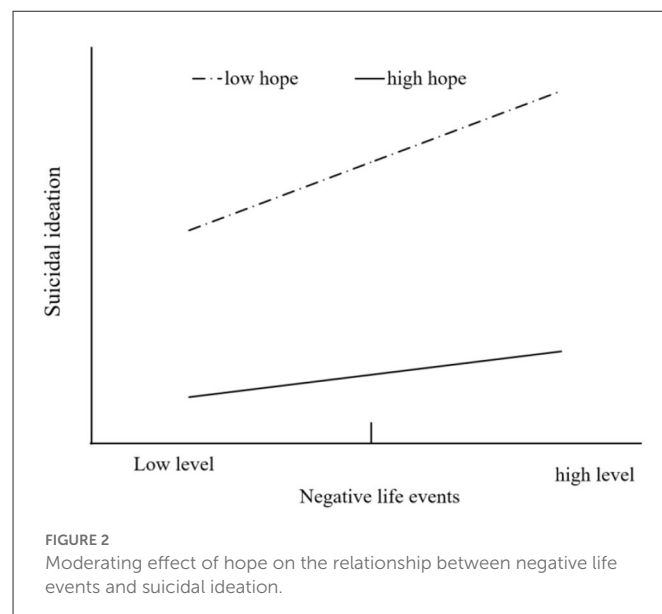
4.2. Buffering effect of hope on risk factors and suicidal ideation

This study explored the influence mechanism of negative life events on suicidal ideation in college students, to seek a feasible direction for crisis intervention efforts. Based on the IMV model of suicidal behavior, we used the moderated mediation model to verify the influence of negative life events on suicidal ideation. It was found that rumination partially mediates the effect of negative life events on suicidal ideation, and the mediating effect is moderated by hope, which provides some ideas for reducing suicidal ideation among college students.

First, rumination was verified to mediate the relationship between negative life events and suicidal ideation, and the mediating effect accounted for 39.89% of the total effect, which reveals the importance of cognitive interventions directed at individuals' cognitions. In the context of the pandemic mitigation period, the challenges of adapting to and integrating into the new environment have become more severe. Faced with negative life events, college students often engage in rumination and focus on negative emotions and thoughts about adverse consequences, which tends to increase suicidal thoughts. Therefore, it is vital to intervene with college students' suicidal ideation from the perspective of their cognitions. For example, helping students gain access to mental health information and resources could reduce their adjustment difficulties, thereby reducing their repeated immersion in negative thinking. In addition, guiding students toward a more rational understanding of the occasional outbreak rather than being trapped in negative and pessimistic emotions, communicating with them timely, and correcting possible

TABLE 5 Results of moderated mediation analysis.

	Suicidal ideation (first step)			Rumination (second step)			Suicidal ideation (second step)			Suicidal ideation (third step)		
	β	t	95% CI	β	t	95% CI	β	t	95% CI	β	t	95% CI
Gender	−0.011	−0.436	[−0.058, 0.037]	0.097	4.002	[0.050, 0.145]	−0.009	−0.372	[−0.057, 0.039]	−0.024	−1.011	[−0.070, 0.022]
Age	−0.020	−4.836	[−0.028, −0.012]	−0.055	−13.271	[−0.064, −0.047]	−0.018	−4.339	[−0.027, −0.010]	−0.013	−3.206	[−0.021, −0.005]
Negative life events	0.127	9.777	[0.101, 0.152]	0.351	27.587	[0.326, 0.376]	0.107	7.877	[0.081, 0.134]	0.077	5.781	[0.051, 0.103]
Rumination							0.202	14.485	[0.175, 0.229]	0.163	11.890	[0.136, 0.190]
Hope	−0.207	−15.932	[−0.233, −0.182]							−0.180	−13.940	[−0.206, −0.155]
Negative life events*Hope	−0.097	−7.771	[−0.121, −0.073]							−0.039	−2.937	[−0.065, −0.013]
Rumination*Hope										−0.134	−10.850	[−0.158, −0.110]
R^2	0.100			0.169			0.085			0.145		
F	114.443			347.885			119.832			123.842		

FIGURE 2
Moderating effect of hope on the relationship between negative life events and suicidal ideation.

cognitive biases and fixations will help to decrease students' suicidal ideation (52). In addition, it is strategically important to understand the practical problems of students and reduce their rumination by exploring more adaptive cognitive strategies.

Second, we found that hope buffered the effect of negative life events on suicidal ideation. Individuals with higher levels of hope are expected to adopt more positive and practical strategies to achieve the desired goals (28). They are able to take a broader perspective and tend to embrace positive reactions to negative life events. Previous studies have demonstrated that activating hope can significantly reduce depressive symptoms (53), which is an important prevention in suicidal ideation. College students may experience excessive stress due to academic and employment preparation, financial difficulties, and strained interpersonal relationships (54). Keeping hope under stressful circumstances may promote the insight that there are difficulties to overcome or targets to achieve (agency), rather than only seeing barriers. In this manner, motivation to deal with stressors may increase, along with the awareness of pathways and the self-confidence and pathways to achieve goals (43). This, in turn, may reduce the painful effects caused by the experience of negative life events and ultimately reduce symptoms of depression and suicidal ideation. Research shows that individuals with high hope levels have higher self-esteem, higher self-efficacy, and better behavior than individuals with low hope levels (31). Hope is a kind of positive mental quality that can offer flexible resources for individuals to effectively respond to risk events, thereby reducing the adverse effects of these events.

It was also found that hope moderated the indirect effect of negative life events on suicidal ideation through the mediating role of rumination. Some scholars have proposed that there are two dimensions of rumination, namely, obsessive thinking and introspection (25). Obsessive thinking is considered maladaptive for the clue that it can lead to the onset of depression, prolong the duration of depression, and worsen the degree of depression. Hope provides a powerful psychological capital that may change the nature of rumination from maladaptive to adaptive. Specifically,

FIGURE 3
Moderating effect of hope on the relationship between rumination and suicidal ideation.
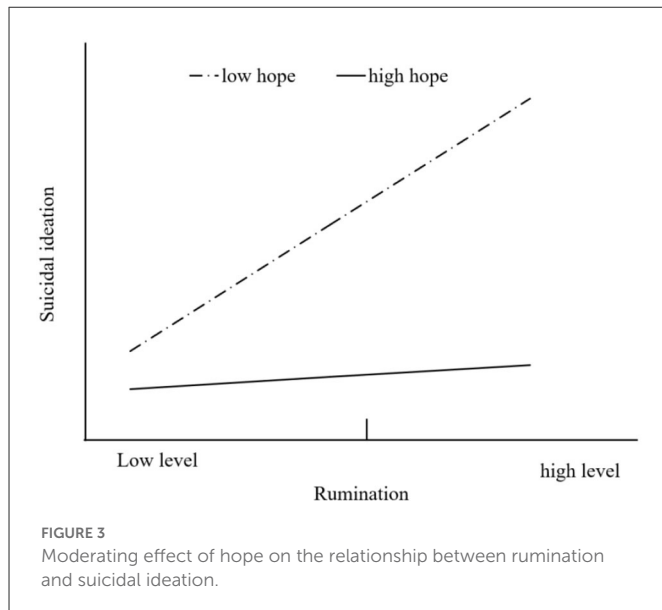
rumination in individuals with high levels of hope is more likely to have a positive adaptive function. Even when there is a non-adaptive obsessive thought (such as "Why can't I do things better"), he actively makes full use of this thinking to generate greater motivation and find better ways to solve problems. Conversely, rumination may have negative and undesirable functions in individuals with low hope. For example, people with low hopes adopt a perturbative approach (e.g., "I was distracted by certain thoughts"), and they will interpret the situation in a negative way. For example, they may think they are incapable of solving the problem and therefore eventually give up. Thus, hope plays an important role in determining whether rumination is adaptive or maladaptive.

4.3. Practical implications

In this study, the strong inverse association between hope and suicidal ideation and its buffering effect predicted the potential value of hope as a target for treatment and intervention. For example, group therapy (55) focused on hope arousal (23) was found to be effective in promoting the level of hope and cultivating students' positive psychological state. As face-to-face activities may be restricted to varying degrees during the pandemic mitigation period, university staff are encouraged to use multimedia platforms to promote the information students need. Targeted online group interventions are encouraged, especially focusing on the cognitive level and specifically targeting rumination, in order to reduce rumination levels and enhance the hope of coping with the difficulties encountered in the new adjustment period. In addition, interpersonal relationships are also an important source of hope. Colleges and universities are encouraged to build a small but intimate social support system with dormitory parks and dormitories as a fulcrum. This can enhance students' sense of belonging and connection. The results provide a positive psychological perspective for the practice of crisis intervention in colleges and universities and additionally provide empirical support for the need for further research on the

positive psychological effects of inspiring students to better with suicidal ideation.

After accounting for the effect of rumination, negative life events can still directly influence suicidal ideation. Cognitive change alone is not enough to prevent suicidal ideation in college students. An important direction for the primary prevention of college students' crises prevention is to guide students to solve realistic problems, make better use of resources, and become familiar with the new environment as soon as possible. During the remission period of the pandemic, colleges and universities should assess the difficulties and challenges faced by college students in advance, sort out the ways of obtaining various resources as fully as possible, provide varied forms of help in the process of students' adaptation, and adjust the enrolment education program to minimize the practical difficulties and realistic pressure faced by students.

4.4. Limitations

Several limitations of our study should be noted. First, cross-sectional studies do not allow us to establish temporal priorities among target variables or to make causal inferences. Therefore, longitudinal studies should further examine the effect of rumination on depression or suicidal ideation in the future. Second, all participants were from Fujian Province, China. However, in terms of outbreak management, it is understood that responses may differ across provinces due to geographical management. The implications of the current conclusions for college students in other provinces in China, and even other countries, need further research. Third, data on incoming college students in the same region prior to the COVID-19 outbreak were not collected, so changes in the mental health status of college students referred to previous studies for baseline comparisons. Follow-up studies would be best used to track changes in suicidal ideation among college students nationwide to better confirm the impact of COVID-19 on mental health status.

5. Conclusion

Our results found that rumination partially mediated the effect of negative life events on suicidal ideation and that hope buffered the direct and indirect effects of negative life events on suicidal ideation, which means that the negative effects of negative life events and rumination on suicidal ideation may be reduced if individuals have higher levels of hope. Based on the results, this study provides practical suggestions for guiding college students' attempts to cope with negative life events, intervening for reflection, cultivating and enhancing students' hope, and providing theoretical support for an approach to the primary prevention of secondary and tertiary interventions with college students who may or are experiencing suicidal ideation during the remission period of the pandemic.

Data availability statement

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

Author contributions

YY designed the study, gathered the data, performed the analysis, and interpreted the data. YY and FD drafted the manuscript. YY, ZQ, FD, and JN revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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

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The relationship between metabolic dysfunction-associated fatty liver disease and the incidence rate of extrahepatic cancer

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Background: The associations between metabolic dysfunction-associated fatty liver disease (MAFLD) and cancer development, especially extrahepatic cancers, are unknown. The aims of the current study were to investigate the cancer incidence rates of MAFLD and analyze the associations between MAFLD and the development of cancers.

Methods: This historical cohort study included participants who underwent ultrasonographic detection of hepatic steatosis at a tertiary hospital in China from January 2013 to October 2021. MAFLD was diagnosed in accordance with *The International Expert Consensus Statement*. Cox proportional hazards regression modeling was used to assess the associations between MAFLD and the development of cancers.

Results: Of the 47,801 participants, 16,093 (33.7%) had MAFLD. During the total follow-up of 175,137 person-years (median 3.3 years), the cancer incidence rate in the MAFLD group was higher than that in the non-MAFLD group [473.5 *vs.* 255.1 per 100,000 person-years; incidence rate ratio 1.86; 95% confidence interval (CI) 1.57−2.19]. After adjustment for age, gender, smoking status, and alcohol status, MAFLD was moderately associated with cancers of the female reproductive system/organs (labium, uterus, cervix, and ovary) [hazard ratio (HR) 2.24; 95% CI 1.09−4.60], thyroid (HR 3.64; 95% CI 1.82−7.30), and bladder (HR 4.19; 95% CI 1.15−15.27) in the total study cohort.

Conclusion: MAFLD was associated with the development of cancers of the female reproductive system/organs (labium, uterus, cervix, and ovary), thyroid, and bladder in the total study cohort.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the main cause of chronic liver disease, with a prevalence of 25.0% worldwide (1) and 29.2% in China (1, 2). The prevalence rates of obesity and diabetes are on the rise. As a result, the prevalence of NAFLD will continue to increase, making NAFLD a growing public health problem (3). NAFLD is a risk factor for morbidity and mortality in liver-related diseases and can cause extrahepatic complications such as metabolic syndrome, type 2 diabetes, cardiovascular disease, and chronic kidney disease (4–7). Previous studies indicated that NAFLD can increase the risk of both intrahepatic and extrahepatic cancers, such as stomach, colorectal, lung, thyroid, and breast (8–11).

In 2020, an international panel of liver disease experts proposed changing the name of NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) and explained the clinical application of this definition in detail (12). The new definition proposes to remove alcohol consumption or the presence of other liver diseases from consideration in the diagnosis of MAFLD. Patients must be diagnosed with hepatic steatosis in addition to being overweight or obese, have type 2 diabetes, or have two or more metabolic risk factors. Therefore, patients with MAFLD may be diagnosed with other chronic liver diseases (12). The definitions of MAFLD and NAFLD are thus not equivalent. In a cohort study from the UK Biobank, which recruited over 500,000 participants aged 40-69 years, the results showed that MAFLD increased cancer risk by approximately 7.0% overall and 59.0% for liver cancer in particular (13). Another cohort study, which also used data from the UK Biobank to explore the association between MAFLD and 24 specific cancers, showed that MAFLD was significantly associated with 10 of the 24 cancers examined, including cancers of the uterus, gallbladder, liver, kidney, thyroid, esophagus, pancreas, bladder, breast, colorectum, and anus (14). Although studies have shown that MAFLD is associated with cancer risk, individual associations with different sites of occurrence have not been conclusively established. The aims of the current study were to assess the incidences of cancer at different sites in patients with MAFLD and compare them with those in a control population.

Materials and methods

Study population and study design

The current historical cohort study included all inpatients diagnosed with MAFLD at the People's Hospital of Guangxi Zhuang Autonomous Region, China, from January 2013 to October 2021 (registration site http://www.chictr.org.cn/index.aspx; registration number ChiCTR2200058543). Briefly, the study used an advanced medical data management system to manage patients and connected and indexed all diagnosis and treatment records held at the hospital. All the medical information assessed was obtained from the electronic database, including demographic characteristics, medical diagnostic codes, surgical codes, drug prescriptions, and death information. When a patient comes to the clinic, the information is automatically integrated into this system.

In the present study, 251,825 patients undergoing liver ultrasound during hospitalization were selected. Those who had a follow-up time at our hospital of <1 year (n = 142,309), lacked information on body mass index (BMI) (n = 5,662), or whose cancer events occurred within 1 year of follow-up (n = 100) were excluded. Patients with a previous history of discharge diagnosis of liver disease, viral hepatitis, kidney disease, malignant tumor, organ transplantation, or radiation therapy were also excluded (n = 38,701). The inclusion and exclusion details are shown in Supplementary Table 1. Ultimately, 47,801 patients were analyzed: 16,093 in the MAFLD group and 31,708 in the non-MAFLD group (Supplementary Figure 1). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki (6th revision, 2008) and was approved by the Ethics Committees of the People's Hospital of Guangxi Zhuang Autonomous Region, China. Individual informed consent was not obtained in this study because we analyzed anonymized electronic medical records data as aggregates, with no individual health data available.

Ascertainment of MAFLD

MAFLD was diagnosed based on abdominal ultrasonography evidence of fatty liver in accordance with the Asia-Pacific Guidelines (15). MAFLD can be diagnosed if fatty liver is diagnosed *via* abdominal ultrasonography and one of the following three conditions exists: 1) overweight or obesity (BMI ≥ 23), 2) diagnosed type 2 diabetes mellitus, or 3) BMI <23 and at least two metabolic risk abnormalities including a) waist circumference ≥90/80 cm, b) blood pressure ≥130/85 mmHg or specific drug treatment, c) plasma triglycerides ≥150 mg/dl (≥1.70 mmol/L) or specific drug treatment, d) plasma HDL-cholesterol <40 mg/dl (<1.0 mmol/L) for men and <50 mg/dl (<1.3 mmol/L) for women or specific drug treatment, e) prediabetes, f) homeostasis model assessment of insulin resistance score ≥2.5 (not included in this

Cancer assessment and covariates

All participants were followed prospectively until death, last medical visit, or December 2022. The International Classification of Diseases–Tenth Revision (ICD-10) codes were used to identify incident cancers (C00–C99). Coding details are shown in Supplementary Table 2. In order to minimize spurious diagnoses, all complete medical records of each individual with C00–C99 codes were reviewed by a physician. The covariates assessed in the study included BMI, diabetes mellitus, hypertension, dyslipidemia, and alcohol and smoking status at baseline. BMI was stratified into normal weight (<23) and overweight and obese (≥23). Hypertension was defined as a history of hypertension, the use of antihypertensive medications, or a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg. Diabetes was defined as a history of diabetes, taking hypoglycemic drugs, or fasting blood glucose ≥7.0 mmol/L, hBA1c ≥6.5. Dyslipidemia was defined as the use of lipid-lowering agents, LDL-cholesterol >100 mg/dl, or triglycerides >150 mg/dl. All laboratory tests were conducted at the People's Hospital of Guangxi Zhuang Autonomous Region, China.

Statistical analysis

Continuous variable baseline data from MAFLD patients and non-MAFLD patients were compared using the Wilcoxon test, and categorical baseline data were compared using the card method. The incidence rates of cancers were calculated by dividing the total number of newly diagnosed cancers by the total number of person-years contributed by people at risk during the follow-up time. Poisson regression modeling was used to estimate the incidence rate ratio (IRR) of cancer progression in the two groups. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the relationships between MAFLD and cancer incidence. Covariate selection was based on a backward selection procedure and other potential confounders identified in the literature (14). In the multivariable analyses, age, gender, smoking status, and alcohol status were adjusted. Stratified analysis by gender was conducted because cancer risks differed between the genders. All reported p-values are two-tailed, and p <0.05 was considered statistically significant. SPSS 18 software (IBM Corp., Armonk, NY, USA) and R software (version 3.3.2, http://www.r-project.org) were used for the statistical analyses.

Results

Baseline characteristics of the study participants

The study included 47,801 participants after the exclusion and inclusion criteria were applied. The prevalence of MAFLD was 33.7% (n = 16,093). Participants in the MAFLD group were older, more likely to be male, more likely to smoke, more likely to be diabetic, and more likely to be hypertensive and/or have dyslipidemia. The levels of fasting glucose, total cholesterol, serum alanine aminotransferase, and gamma-glutamyl transferase were higher in the participants with MAFLD. The baseline characteristics of the study participants are summarized in Table 1.

Incidence rates of cancer

The follow-up period (median 3.3 years, interquartile range 2.0–5.1 years) included 175,137 person-years of follow-up. Malignancies were newly diagnosed in 291 participants (1.81%) with MAFLD and 290 participants (0.91%) without MAFLD. In the MAFLD group, the overall cancer incidence rate was 473.5 (95% CI 420.6–531.1) per 100,000 person-years, which was significantly higher than that in the non-MAFLD group which was 255.1 (95% CI 226.6–286.2) per 100,000 person-years (IRR 1.86, 95% CI 1.57–2.19) (Table 2).

In the MAFLD group, the incidence rates of nine specific cancers were significantly higher than those in the non-MAFLD group, including cancers of the duodenum, colon, and rectum (IRR 1.65, 95% CI 1.10–2.47); breast (IRR 1.95, 95% CI 1.02–3.72); female reproductive system/organs (labium, uterus, cervix, and ovary) (IRR 2.28, 95% CI 1.15–4.61); prostate (IRR 1.96, 95% CI 1.01–3.80); thyroid (IRR 2.14, 95% CI 1.11–4.18); renal pelvis (IRR 4.16, 95% CI 1.16–18.49); bladder (IRR 6.17, 95% CI 1.59–34.86); and brain and central nervous system (IRR 4.32, 95% CI 1.12–16.69) (Table 2).

With respect to gender, the incidence rate of thyroid cancer in the male participants in the MAFLD group was significantly higher than that in the non-MAFLD group (IRR 3.89, 95% CI 1.07–14.14), but in the female participants, the incidence rates of thyroid cancer did not differ significantly in the two groups. In the female participants, the MAFLD group had significantly higher incidence rates of cancers of the stomach (IRR 3.13, 95% CI 1.05–9.30), lung (IRR 3.01, 95% CI 1.54–5.91), skin (IRR 10.72, 95% CI 1.20–95.88), breast (IRR 2.99, 95% CI 1.56–5.76), and female reproductive system/organs (labium, uterus, cervix, and ovary) (IRR 3.31, 95% CI 1.75–6.27) (Supplementary Table 3). The cumulative incidence of all cancers is shown in Supplementary Figure 2.

Association between MAFLD and cancer risk

In the univariate analysis, participants in the MAFLD group had a higher risk of all cancers than those in the non-MAFLD group (HR 1.79, 95% CI 1.52–2.10), and the result was consistent after adjustment for age, gender, smoking status, and alcohol status (HR 1.35, 95% CI 1.15–1.60) (Table 3). At different cancer sites, MAFLD was significantly associated with cancers of the female reproductive organ (labium, uterus, cervix, and ovary) (HR 2.24, 95% CI 1.09–4.60), thyroid (HR 3.64, 95% CI 1.82–7.30), and bladder (HR 4.19, 95% CI 1.15–15.27) in the total study cohort. In the subgroup

TABLE 1 Baseline characteristics of the study participants.

Characteristics	Total (n = 47,801)			Male participants (n = 19,477)			Female participants (n = 28,324)		
	Non-MAFLD (n = 31,708)	MAFLD (n = 16,093)	p-value	Non-MAFLD (n = 10,625)	MAFLD (n = 8,852)	p-value	Non-MAFLD (n = 21,083)	MAFLD (n = 7,241)	p-value
Age (years)	45 (32–62)	60 (50–68)	<0.001	60 (46–69)	58 (48–67)	<0.001	37 (30–55)	62 (52–70)	<0.001
Gender, male (%)	10,625 (33.51%)	8,852 (55.01%)	<0.001			<0.001			<0.001
BMI	22.43 (20.20–24.77)	25.72 (23.94–27.89)	<0.001	22.66 (20.69–24.61)	25.95 (24.22–27.99)	<0.001	22.22 (19.99–24.89)	25.48 (23.62–27.77)	<0.001
Smoking, n (%)			<0.001			<0.001			<0.001
Never	28,410 (89.60%)	12,901 (80.17%)	<0.001	7,413 (69.77%)	5,748 (64.93%)	<0.001	20,997 (99.59%)	7,153 (98.78%)	<0.001
Current	1,874 (5.91%)	2,125 (13.20%)	<0.001	1,808 (17.02%)	2,057 (23.24%)	<0.001	66 (0.31%)	68 (0.94%)	<0.001
Past	1,424 (4.49%)	1,067 (6.63%)	<0.001	1,404 (13.21%)	1,047 (11.83%)	<0.001	20 (0.09%)	20 (0.28%)	<0.001
Alcohol, n (%)			<0.001			<0.001			<0.001
Never	29,695 (93.65%)	13,932 (86.57%)	<0.001	8,664 (81.54%)	6,758 (76.34%)	<0.001	21,031 (99.75%)	7,174 (99.07%)	<0.001
Current	1,553 (4.90%)	1,696 (10.54%)	<0.001	1,507 (14.18%)	1,665 (18.81%)	<0.001	46 (0.22%)	31 (0.43%)	<0.001
Past	460 (1.45%)	465 (2.89%)	<0.001	454 (4.27%)	429 (4.85%)	<0.001	6 (0.03%)	36 (0.50%)	<0.001
Fasting glucose (mmol/L)	4.50 (4.13–4.98)	5.05 (4.54–6.08)	<0.001	4.61 (4.22–5.14)	5.06 (4.54–6.19)	<0.001	4.45 (4.08–4.89)	5.03 (4.54–5.94)	<0.001
Diabetes, n (%)	2,705 (8.53%)	4,479 (27.83%)	<0.001	1,546 (14.55%)	2,508 (28.33%)	<0.001	1,159 (5.50%)	1,971 (27.22%)	<0.001
Hypertension, n (%)	7,893 (24.89%)	8,996 (55.90%)	<0.001	4,040 (38.02%)	5,043 (56.97%)	<0.001	3,853 (18.28%)	3,953 (54.59%)	<0.001
Dyslipidemia, n (%)	2,736 (8.63%)	5,025 (31.22%)	<0.001	1,384 (13.03%)	2,925 (33.04%)	<0.001	1,352 (6.41%)	2,100 (29.00%)	<0.001
ALT (U/L)	13 (10–19)	20 (14–29)	<0.001	17 (13–25)	23 (16–33)	<0.001	12 (9–16)	17 (13–24)	<0.001
AST (U/L)	19 (16–23)	21 (17–26)	<0.001	21 (17–26)	22 (18–27)	<0.001	18 (15–22)	20 (17–24)	<0.001
GGT (U/L)	17 (12–27)	29 (21–46)	<0.001	26 (18–42)	36 (25–56)	<0.001	14 (11–20)	23 (17–34)	<0.001
TC (mmol/L)	4.74 (3.99–5.65)	4.91 (4.17–5.70)	<0.001	4.49 (3.80–5.27)	4.80 (4.05–5.58)	<0.001	4.92 (4.13–5.87)	5.04 (4.31–5.82)	<0.001
HDL-cholesterol (mmol/L)	1.29 (1.06–1.59)	1.09 (0.93–1.27)	<0.001	1.13 (0.95–1.35)	1.02 (0.88–1.19)	<0.001	1.42 (1.17–1.72)	1.17 (1.01–1.37)	<0.001
LDL-cholesterol (mmol/L)	2.87 (2.33–3.50)	3.06 (2.51–3.64)	<0.001	2.82 (2.28–3.41)	3.02 (2.47–3.59)	<0.001	2.91 (2.36–3.56)	3.12 (2.56–3.70)	<0.001
TG (mmol/L)	1.16 (0.82–1.81)	1.67 (1.21–2.38)	<0.001	1.12 (0.82–1.57)	1.70 (1.21–2.47)	<0.001	1.19 (0.81–2.06)	1.65 (1.21–2.29)	<0.001

Values are expressed as median (Q1–Q3) or number (%).
BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; MAFLD, metabolic dysfunction-associated fatty liver disease.

TABLE 2 Cancer incidence rates in participants with and without MAFLD.

Cancer site	Number of cancers	Cancer incidence rates per 100,000 person-years				p-value
		All	MAFLD	Non-MAFLD	IRR (95% CI)	
All cancers	581	331.7	473.5	255.1	1.86 (1.57, 2.19)	<0.001
Oral cavity	6	3.4	6.5	1.8	3.70 (0.53, 40.90)	0.105
Pharynx	21	12.0	14.6	10.6	1.39 (0.52, 3.59)	0.456
Esophagus	11	6.3	3.3	7.9	0.41 (0.04, 1.99)	0.240
Stomach	37	21.1	22.8	20.2	1.13 (0.54, 2.28)	0.726
Duodenum, colon, and rectum	104	59.4	79.7	48.4	1.65 (1.10, 2.47)	0.010
Liver	30	17.1	22.8	14.1	1.62 (0.73, 3.54)	0.184
Biliary	8	4.6	8.1	2.6	3.08 (0.60, 19.85)	0.104
Pancreas	12	6.9	11.4	4.4	2.59 (0.71, 10.35)	0.092
Spleen	4	2.3	4.9	0.9	5.55 (0.45, 291.31)	0.095
Laryngeal	6	3.4	8.1	0.9	9.25 (1.03, 437.42)	0.013
Lung	105	60.0	74.8	51.9	1.44 (0.96, 2.16)	0.061
Skin	9	5.1	11.4	1.8	6.47 (1.23, 63.87)	0.007
Breast	37	21.1	30.9	15.8	1.95 (1.02, 3.72)	0.042
Labium, uterus, cervix, and ovary	38	21.7	34.2	15.0	2.28 (1.15, 4.61)	0.009
Prostate	35	20.0	29.3	15.0	1.96 (1.01, 3.80)	0.047
Renal pelvis	13	7.4	14.6	3.5	4.16 (1.16, 18.49)	0.010
Bladder	13	7.4	16.3	2.6	6.17 (1.59, 34.86)	0.002
Brain and central nervous system	10	5.7	11.4	2.6	4.32 (1.12, 16.69)	0.034
Thyroid	41	23.4	35.8	16.7	2.14 (1.11, 4.18)	0.013
Non-Hodgkin's lymphoma	20	11.4	11.4	11.4	1.00 (0.34, 2.69)	0.993
Leukemia	14	8.0	13.0	5.3	2.47 (0.75, 8.62)	0.084

Overall follow-up duration: 175,137 person-years; non-MAFLD group follow-up duration: 113,678 person-years; MAFLD group follow-up duration: 61,459 person-years.
CI, confidence interval; IRR, incidence rate ratio; MAFLD, metabolic dysfunction-associated fatty liver disease.

analysis by gender, the results were consistent, with the exception of bladder cancer (Supplementary Table 4).

Discussion

In this retrospective cohort study, the relationships between MAFLD and different cancer types were analyzed. MAFLD was associated with higher incidence rates of cancers, particularly extrahepatic-specific cancers of the bladder, thyroid, and female reproductive system/organs (labium, uterus, cervix, and ovary). As MAFLD is a new definition, cohort studies on the relationship between MAFLD and cancer are scarce, with only two cohort studies from the UK Biobank database. The UK Biobank is a large-scale, population-based prospective cohort study that recruited over 0.5 million participants aged 40-69 years in 2006-2010 and combined extensive measurements of baseline data and genotype data with linked national medical records for longitudinal follow-up (13). One study selected 423,252 participants who were diagnosed with MAFLD. During the median follow-up of 8.2 years,

compared with participants without MAFLD, those with MAFLD had a multivariate-adjusted HR of 1.07 (95% CI 1.05–1.10) for all cancers and 1.59 (95% CI 1.28, 1.98) for liver cancer (13). The other study included 352,911 participants, with 37.2% diagnosed as MAFLD, and during the median follow-up of 8.2 years, compared with non-MAFLD, MAFLD was significantly associated with 10 of the 24 examined cancers, including corpus uteri (HR = 2.36, 95% CI 1.99–2.80), gallbladder (2.20, 1.14–4.23), liver (1.81, 1.43–2.28), kidney (1.77, 1.49–2.11), thyroid (1.69, 1.20–2.38), esophagus (1.48, 1.25–1.76), pancreas (1.31, 1.10–1.56), bladder (1.26, 1.11–1.43), breast (1.19, 1.11–1.27), and colorectal and anus cancers (1.14, 1.06–1.23) (14). The results of this study are mostly consistent with the two UK Biobank cohort studies, except for liver cancer. In this present study, there was no significant relationship between MAFLD and liver cancer. The discrepancy may be related to differences in study populations in the two studies. The UK Biobank study recruited a representative sample of the general population based on ethnic and sociodemographic data, with an equal proportion of men and women and a balanced population between the ages of 40 and 69 years over a 5-year

TABLE 3   Association between MAFLD and the development of cancers.

Cancer site	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
All cancers	1.79 (1.52, 2.10)	<0.001	1.32 (1.12, 1.55)	0.001
Oral	3.57 (0.65, 19.50)	0.142	2.41 (0.43, 13.60)	0.321
Pharynx	1.32 (0.56, 3.14)	0.525	1.01 (0.42, 2.44)	0.978
Esophagus	0.40 (0.09, 1.85)	0.239	0.30 (0.06, 1.38)	0.122
Stomach	1.08 (0.55, 2.09)	0.825	0.76 (0.39, 1.49)	0.424
Duodenum, colon, and rectum	1.57 (1.06, 2.31)	0.023	1.09 (0.74, 1.61)	0.652
Liver	1.53 (0.75, 3.13)	0.246	1.06 (0.51, 2.17)	0.881
Pancreas	2.54 (0.81, 8.01)	0.112	1.87 (0.59, 5.95)	0.288
Spleen	5.56 (0.58, 53.47)	0.138	3.93 (0.41, 38.02)	0.238
Laryngeal	8.45 (0.99, 72.36)	0.051	5.03 (0.59, 43.11)	0.140
Lung	1.38 (0.94, 2.03)	0.101	0.94 (0.64, 1.38)	0.741
Skin	6.26 (1.30, 30.16)	0.022	4.62 (0.95, 22.38)	0.057
Breast	1.91 (1.00, 3.64)	0.049	1.77 (0.89, 3.53)	0.106
Labium, uterus, cervix, and ovary	2.09 (1.10, 3.99)	0.025	2.24 (1.09, 4.60)	0.029
Prostate	1.88 (0.97, 3.64)	0.063	1.46 (0.75, 2.85)	0.263
Renal pelvis	4.11 (1.27, 13.36)	0.019	2.85 (0.87, 9.32)	0.084
Bladder	5.86 (1.61, 21.31)	0.007	4.19 (1.15, 15.27)	0.030
Brain and central nervous system	4.26 (1.10, 16.49)	0.036	3.73 (0.92, 15.10)	0.065
Thyroid	2.08 (1.13, 3.85)	0.019	3.64 (1.82, 7.30)	0.000
Non-Hodgkin's lymphoma	0.96 (0.38, 2.42)	0.939	0.71 (0.28, 1.79)	0.466
Leukemia	2.35 (0.81, 6.77)	0.114	1.79 (0.61, 5.26)	0.292

Hazard ratios and p-values represent the MAFLD group compared with the non-MAFLD group, ascertained via Cox proportional hazards regression modeling. Multivariable analyses were adjusted for age, gender, smoking status, and alcohol status.
CI, confidence interval; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease.

period (16, 17), whereas our study data were derived from a hospital patient population.

MAFLD is defined differently from NAFLD, which excludes liver-related diseases. The exclusion of other causes such as drug-induced hepatitis, viral hepatitis, alcoholism, and other liver diseases is not a requirement for MAFLD (18). The definition of MAFLD covers the systemic risk associated with fatty liver disease, whereas NAFLD focuses on liver-related factors. Therefore, given the strong association between MAFLD and the established risk factors for these diseases, it is not surprising that MAFLD is associated with an increased risk of both intrahepatic and extrahepatic events (13). Currently, the definition of MAFLD is somewhat controversial in the field of liver disease (19, 20). A meta-analysis showed that MAFLD was not a replacement for NAFLD and that there were significant differences in the prevalence and risk factors between them (21). MAFLD was proposed as an alternative definition in an effort to improve people's awareness, especially primary care doctors, and to better summarize metabolic dysfunction (22).

In the current study, MAFLD was moderately associated with cancers of the female reproductive system/organs (labium, uterus, cervix, and ovary), bladder, and thyroid in the total study cohort. MAFLD increases the risks of obesity, diabetes, and hypertension, in turn increasing the burden of metabolism-related diseases (21). In the present study, the MAFLD group had a higher median BMI than the non-MAFLD group, and the prevalence rates of diabetes, hypertension, and dyslipidemia were also higher in the MAFLD group. Studies on hypertension and cancer indicate that patients with hypertension have a significantly higher risk of cancer than non-hypertensive patients, particularly with respect to colorectal cancer and breast cancer (23–25). In a two-sample Mendelian randomization study, there were causal detrimental effects of type 2 diabetes on cancer of the uterus, kidney, pancreas, and lung (26). Dyslipidemia and obesity are evidently risk factors for most cancer types (27, 28). This may explain why the cancer incidence rate was significantly higher in the MAFLD group in the current study. The precise pathophysiological mechanisms that link MAFLD and cancers are unknown, and further studies are needed to elucidate

these links. Moreover, there may be significant implications for cancer screening and surveillance strategies in MAFLD patients given the growing number of patients with MAFLD.

The strength of the present study is that it is the first large cohort study to explore the association between MAFLD and cancer in western China. However, there are some limitations to this study. First, the participants of this study were derived from a hospital patient population, so the potential selection bias was unavoidable. Second, fatty liver was diagnosed using abdominal ultrasound rather than liver biopsy. Ultrasound has limited sensitivity, and it could result in steatosis with less than 20% of fatty liver individuals that cannot be detected (29, 30). However, due to its invasive nature, liver biopsy is not feasible in large population-based studies. Third, the follow-up time of this study was short (median 3.3. years), leading to outcome events that could not be observed. In addition, the small numbers of some site-specific cancers may have resulted in the instability of the results. Thus, a longer follow-up is required to verify the results. Fourth, the parameters used to assess the diagnosis of MAFLD, such as waist circumference, insulin, oral glucose tolerance test, and hsCRP, are missing in this study. This may have resulted in some MAFLD cases being missed and MAFLD may have misclassification in some participants. So, we will construct a long-term follow-up of a prospective cohort study that has complete baseline data to avoid this bias. Fifth, cancer cases were identified by ICD-10 codes, which may be associated with misclassification or underreporting. Sixth, the pathological severity of hepatic steatosis was not collected in this study. Lastly, metabolic abnormalities may change with the state of the participants, so the metabolic state at baseline may not accurately reflect the true metabolism of the individual.

Conclusion

In this retrospective cohort study, MAFLD was associated with an increased risk of cancer. The study suggests that multidisciplinary assessment is required and attention should be paid to the development of malignancy in patients with MAFLD.

Data availability statement

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

Ethics statement

This study was performed in accordance with the principles outlined in the Declaration of Helsinki and approved by the People's Hospital of Guangxi Zhuang Autonomous Region Ethics Committee and the Institutional Review Board. Individual informed consent was not obtained in this study because we analyzed anonymized electronic medical records data as aggregates, with no individual health data available.

Author contributions

SW and JY conceived and designed the study and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.985858/full#supplementary-material

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