Perspectives in Public Health

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East Sussex Nursery Transformation Programme (2015–2020): embedding a best practice approach to healthy food in early years settings

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East Sussex Nursery Transformation Programme (2015-2020) - embedding a best practice approach to healthy food in early years settings

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Abstract:	The East Sussex Nursery Transformation Programme aims to transform health and wellbeing outcomes for children and their families. Primarily focused on reducing childhood obesity and implemented across the county since 2015, this unique partnership between the local authority, clinical commissioning groups and early years settings was designed to support settings to adopt and embed a whole setting approach to health and wellbeing (including healthy eating). This article summarises the programme and details the impact on participating settings' approach to and provision of food during the 2017-2019 programme years, highlighting the key role early years settings play in developing healthy eating habits in early childhood.

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East Sussex Nursery Transformation Programme (2015-2020) - embedding a best practice approach to healthy food in early years settings

The East Sussex Nursery Transformation Programme aims to transform health and wellbeing outcomes for children and their families. Primarily focused on reducing childhood obesity and implemented across the county since 2015, this unique partnership between the local authority, clinical commissioning groups and early years settings was designed to support settings to adopt and embed a whole setting approach to health and wellbeing (including healthy eating). This article summarises the programme and details the impact on participating settings' approach to and provision of food during the 2017-2019 programme years, highlighting the key role early years settings play in developing healthy eating habits in early childhood.

Introduction

The role of early years settings in helping to provide and promote a healthy diet in early childhood and prevent obesity has been highlighted internationally and nationally.[1,2] Research suggests the educational context within which food is provided powerfully influences eating behaviour.[Error! Bookmark not defined.] Systematic reviews of interventions in childcare settings indicate multi-component, multi-level interventions focusing on the childcare environment, policies and practices, staff training and personal health, child engagement and parental support are most effective in preventing obesity.[3] The East Sussex Nursery Transformation Programme (NTP) has applied this growing evidence base to improve food provision and practices in local early years settings. Funded by East Sussex County Council (ESCC) Public Health (and by NHS Eastbourne, Hailsham and Seaford and Hastings and Rother Clinical Commissioning Groups (CCGs) during 2016/17), the NTP is an integral component of the Council's whole-systems healthy weight plan.[4]

In England, all regulated early years settings must follow the mandatory standards of the Early Years Foundation Stage framework,[5] including that meal, snack and drink provision must be '*healthy, balanced and nutritious*'. Voluntary Food and Drink Guidelines for Early Years Settings in England ('the guidelines')[6] and Government's example menus for early years settings in England[7] help settings meet these requirements. The RSPH-accredited Eat Better, Start Better (EBSB) training and evaluation programme[8] was developed to support early years settings to implement the guidelines using a whole-setting approach to food. ESCC was involved in the

Government-subsidised roll out of the EBSB programme in 2012-13[8] and has continued to offer EBSB training as part of the NTP.

The Nursery Transformation Programme

The NTP, known locally as the 'Healthy Active Little Ones' (HALO) programme, has been implemented over four phases. The first phase (2015-2016),[9] was undertaken as a successful 18-month workforce development and intervention pilot. The pilot evaluation informed a second phase (2016-17), which enabled 140 settings (located within two CCG funded areas) to access a grant of up to £5,000 to fund evidence-based activities to prevent obesity and promote oral health. During a third phase (2017-19), 204 settings accessed a further £3,000 grant. In October 2019, the programme was expanded to include additional health and wellbeing topics and has focused on embedding best practice and building workforce capacity to ensure a sustainable programme.

To receive a grant during the 2016-17 and 2017-19 programme years, settings had to participate in a baseline and six/nine-month follow up audit, known as a HALO Healthy Eating and Physical Activity Check ('HALO Check'). This was facilitated by a trained, independent Healthy Eating and Physical Activity (HEPA) co-ordinator employed by ESCC. The healthy eating component of the HALO Check evaluated each setting's approach to food and nutrition against national best practice guidance, and their food provision against the guidelines.[6]

With support from a HEPA co-ordinator, settings were then required to submit a Grant Expenditure Proposal (GEP), based on needs identified in their HALO Check, which was subsequently approved by a local authority panel. Settings were encouraged to use their grant to fund a range of evidenced-based healthy eating interventions/workforce development opportunities that had been successfully tried and tested during the pilot. The EBSB offer for settings included a one-day or half-day food, nutrition and healthy cooking with children and families course; annual membership for three online early years food and nutrition courses;[10] and application for, or renewal of an Outstanding Food Award. Each setting was given six to nine months to apply the knowledge and skills they had acquired through participating in the EBSB initiatives and the support received from their HEPA co-ordinator to implement changes to their food practices and provision. The outcomes and impact of the changes made were documented in their follow-up HALO Check.

During the first three programme phases, ESCC Public Health also commissioned local authority EBSB support which included:

- Training and support from a Registered Nutritionist for the HEPA co-ordinators, focusing on consistency in completion of HALO Checks.
- An evaluation of the impact of the NTP on participating settings' approach to and provision of food.

Changes in settings' approaches to food and food provision

During the 2017-19 programme years, baseline and 9-month follow up HALO Checks were completed for 180 settings, 64% of which had been involved in one or more previous phases of the programme (2015-16 and/or 2016-17).

Changes in approach to food and nutrition

The guidelines[6] specify 38 best practice recommendations for approach to food and nutrition. Analysis of HALO Checks found that 96% of settings either increased (69%) or maintained (27%) the number of recommendations 'fully met' between baseline and follow up. The mean number of recommendations 'fully met' in each setting significantly increased from 32.8 (Standard deviation (SD)=4.8) at baseline to 35.9 (SD=3.0) at follow up (paired samples t-test; $t(179)=-10.88, p<0.001$). Settings involved in previous phases of the NTP met significantly more recommendations at follow up, (one-way ANOVA; $F=9.81$, $p<0.001$), with 46 settings who had participated in all three programme phases increasing the mean number of recommendations met at each phase, demonstrating continued improvement. The main changes observed were the development of comprehensive food policies in consultation with staff, parents, and children; communicating with families about the timing of meals; giving children an opportunity to help plan menus, and for families to give feedback on the food provided, and increased engagement with parents and children around food activities.

Changes in food provision

The guidelines specify 79 best practice recommendations for food provision.[6] Analysis of HALO Checks showed 72% of the settings increased (48%) or maintained (24%) the percentage of applicable guidelines 'fully met' between their baseline and follow up, with over a third (37%) fully meeting all guidelines applicable to the meals and snacks they provided by follow up. The mean number of applicable guidelines 'fully met' increased from

47.4 (SD=17.7) at baseline to 51.0 (SDS=16.1) at follow up (representing between 94.0% and 95.8% of applicable guidelines being met depending on programme phase). The results demonstrate a positive shift in the nutritional quality of meals and snacks provided (despite revisions to the guidelines made in 2017 making them more challenging to meet).[7] In particular there was increased fruit and vegetable provision at breakfast, more variety of foods provided, and an increased use of products lower in salt and sugar.

Recommendations

Early childhood has been identified as a critical time for obesity prevention and early years settings have a key role to play. The evaluation of the East Sussex NTP has demonstrated that with investment and ongoing support, settings can continually improve their approach to, and provision of food. Given the scale of childhood obesity, it is recommended that other local authorities consider how elements of the East Sussex NTP could be replicated. Current programme information, including amendments resulting from the COVID-19 pandemic are available at https://czone.eastsussex.gov.uk/early-years/halo/. Adopting the NTP unique collaborative partnership approach would empower and enable childcare providers to become 'health promoting settings' supporting them to fulfil their role in encouraging the development of healthy eating behaviours, giving children the best start in life.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Improving access to oral healthcare for people experiencing homelessness is good for public health

Witton, Robert

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Improving access to oral healthcare for people experiencing homelessness is good for public health

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Homelessness in countries with developed economies remains a significant challenge[1]. In the UK, at least 320,000 people[2] are currently estimated to live in temporary accommodation or on the streets while an increase in the number of young people and families living in temporary or overnight accommodation has been reported[3]. Homelessness is associated with increased morbidity and mortality[2]. Dental problems are among the most common health concerns affecting people experiencing homelessness, with higher levels of untreated dental disease and more missing teeth than in the general population, causing poorer oral health related quality of life[3,4]. In addition, the lived experience of homelessness and characteristics of the healthcare system contribute to low uptake of dental services[5].

A study in London involving 260 people revealed that 60% of the participants had suffered from toothache since they became homeless, while 15% had pulled out their own teeth[5]. A number of organisations have called for better access to oral healthcare for people experiencing homelessness[5,6] and the NHS Long Term Plan specifically mentions people experiencing homelessness as a priority group[7]. However, despite this there are very few dedicated dental services across the UK that cater for the needs of this group and very little prioritisation for their development. The purpose of this article is to improve awareness of the need to include and integrate oral healthcare into initiatives and programmes that support people experiencing homelessness and explain why doing this is good for public health.

What are the issues?

People experiencing homelessness can have precarious living conditions making the routine of attending appointments difficult. This effectively excludes them from mainstream high street dental services where dental practices operate as small businesses and rely on regular attendance of patients to maintain financial viability. In addition, some people experiencing homelessness can have high treatment needs and due to its design the current NHS dental contract can disincentive dentists and practices from accepting patients that

need extensive treatment. In some areas community dental services may accept people experiencing homelessness or there may be ad hoc services offering access, usually for a single course of urgent care only but these are highly variable across the UK making access to care a postcode lottery.

Without access to dental services, the healthcare system is bearing a considerable indirect cost due to attendance at the GP for dental pain and sepsis, inappropriate presentations at A&E and repeat prescriptions of antibiotics and analgesia by GP outreach services[2,5]. These healthcare costs are avoidable and expensive and often fail to address the dental problem. They also encourage the use of antibiotics for acute dental conditions that often require a surgical intervention to resolve, at a time when anti-microbial resistance is a global public health challenge.

What works?

Efforts to improve equity in access to oral healthcare for people experiencing homelessness requires significant change in healthcare policy and fundamental change in commissioning philosophy and approach that recognises a 'one size fits all' dental service model does little to address oral health inequalities in this group and in many others. Development of new services should be done in a way that recognises homeless peoples' complex and diverse needs, and is fully integrated into the wider public health and healthcare response to avoid oral health being seen as an optional 'nice to have'.

There is information available in the UK to help in the design of dental services for people experiencing homelessness and a common set of enablers are emerging[8,9,10,12]. Outreach and community engagement can often help to break down barriers to care by meeting people in their own environment, this can help to de-stigmatize the view of healthcare professionals and build positive relationships that are based on trust[12]. The importance of

community engagement is also increasingly recognised in healthcare education. There is a need to educate the next generation of healthcare professionals to have a greater understanding of the complex circumstances that result in many groups in society experiencing vulnerability and why their access to healthcare services is low[13]. The role of link workers is a key enabler and effective communication and co-ordination between the dental service and the day or residential centre is vital for minimising lost clinical time and encouraging/reminding of attendance. Improving support workers awareness of the importance of oral health can also better support patients' behaviour change journey[11,12]. In terms of the dental service itself, non-judgmental and empathetic staff are integral to facilitating access and a relaxed and friendly atmosphere with good communication and clear expectations for both parties can help to build positive relationships for ongoing care[12]. Perhaps the most important factors are flexibility and personalised care. Being able to respond to patients as individuals is challenging for providers but essential to build a successful service[8,9,10,12]. Providing longer appointments, availability of appointments at short notice and being able to offer appointments to complete treatment in as short a time as possible can all influence service outcomes.

Evidence demonstrates that oral health interventions can improve a homeless person's quality of life and become a significant part of their journey towards stability[8,10,12]. A recent service evaluation of a homelessness dental service in the southwest[12] reported perceived improvements in oral health measures (oral hygiene), physical health (enhanced nutrition), psycho-social health (improved confidence and self-esteem, happiness and improved body image) and economic impacts (leading to employment, life aspirations and wider engagement with other services). Improving oral health in people experiencing homelessness can be an important catalyst to wider change in multiple areas of a person's life and should be regarded as an essential healthcare need alongside others.

Conclusion

Improving access to oral healthcare for people experiencing homelessness is part of the effort to address health inequities and inequalities that exist in the health care system. There is growing evidence in the UK of highly effective models of care that improve access in a way that is acceptable patients and to healthcare professionals. The challenge is to develop flexible commissioning models that address and prioritise the unique oral healthcare needs of this group in a way that is more equitable and sustainable across the UK.

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Addressing the under-representation of ethnic minority groups in COVID-19 vaccine trials

In this article, Richard Armitage addresses how ethnic minority individuals are significantly under-represented in UK COVID-19 vaccine trials. While the causes are multifactorial, this disparity must be urgently addressed for safety and efficacy to be demonstrated in, and the resulting product to be deemed acceptable to, members of these communities.

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Vaccines against COVID-19 are widely considered to be the only viable pandemic exit strategy. As such, numerous vaccines have received Emergency Use Authorisation and are currently being offered to priority groups in the UK according to advice from the Joint Committee on Vaccination and Immunisation,[1] with over 20 million first doses having being administered at the time of writing (4 March 2021).[2] Prior to their authorisation, each candidate vaccine underwent a double-blind, placebo-controlled, randomised trial involving human participants to assess their safety and efficacy for use at scale. Many of these trials took place, and continue to proceed, in the UK.

As with all clinical trials, participants in vaccine studies should be representative of the populations for whom the intervention is intended. This is of particular salience to members of minority ethnic communities, which have been disproportionately affected by the COVID-19 pandemic.[3] Despite this, ethnic minority individuals are being vaccinated against COVID-19 at lower rates than White people,[4] even among some National Health Service (NHS) employees.[5] While the causes of these disparities are complex and multifactorial, the under-representation of ethnic minority groups in COVID-19 vaccine trials may provide part of the explanation.

So far, over 368,000 volunteers have been enrolled into UK COVID-19 vaccine trials.[6] However, only 7.4% of these participants belong to ethnic minorities, including 0.6% and 4.2% from Black and Asian backgrounds, respectively.[2] This is while ethnic minorities account for 17.5% of the total population in England and Wales, including 3.4% and 7.5% from Black and Asian backgrounds, respectively.[7] This disparity led Equalities Minister Kemi Badenoch to urge more people from ethnic minorities to take part in vaccine trials.[8]

The under-representation of ethnic minority groups in health research is recurrent, complex, and multifactorial. Barriers to participation in research include language challenges, low research awareness, mistrust of researchers, stigma, cultural values, beliefs about research, poor engagement from researchers, and socioeconomic limitations, as well as hesitancy on the part of participants.[9] However, it is of paramount importance that these communities are proportionally represented in COVID-19 vaccine trials for safety and efficacy to be demonstrated in, and the resulting product to be deemed acceptable to, individuals belonging to these groups.

So far, over 368,000 volunteers have been enrolled into UK COVID-19 vaccine trials. However, only 7.4% of these participants belong to ethnic minorities, including 0.6% and 4.2% from Black and Asian backgrounds, respectively

While strong evidence for effective strategies to improve recruitment in ethnic minority communities is lacking, the National Institute of Health Research's (NIHR) toolkit provides useful suggestions, such as researchers and health professionals fostering cultural competency throughout all stages of research.[10] Such strategies have also been identified as essential to the

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successful roll-out of the COVID-19 vaccination programme itself.[11] The call-to-action from Kemi Badenoch, who herself belongs to an ethnic minority group, along with her publicly celebrated participation in a vaccine trial,[3] is another example of a powerful strategy which could be amplified and replicated by influential leaders within ethnic minority communities to promote trust and enhance recruitment.

Although the race to vaccinate the UK population against COVID-19 is well underway, numerous clinical trials continue to progress, for both those vaccines already authorised for emergency use, and those not yet approved for distribution. It is vitally important that all groups are adequately included in these trials to ensure confidence is fostered in the safety and efficacy profiles of the products they are due to receive. This is especially the case for ethnic minority communities in light of the ethnic disparities so far seen in COVID-19 outcomes and vaccine uptake rates. Such action will require a collaborative, coordinated, responsible approach from researchers, funders, public health professionals, policy agencies, and ethnic minority communities themselves. The call from the Royal College of General Practitioners for a high-profile campaign backed by faith leaders and prominent figures from ethnic minority communities to increase vaccine uptake among ethnic minorities is an excellent opportunity for meaningful health promotion that could translate to improved outcomes for marginalised people and inspire similar action by other influential groups.[12]

It is vitally important that all groups are adequately included in these trials to ensure confidence is fostered in the safety and efficacy profiles of the products they are due to receive

As hopes begin to glimmer for a return towards something resembling normalcy, the current under-representation of ethnic minority groups in COVID-19 vaccine trials must be urgently addressed.

CONFLICT OF INTEREST

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Ending weight-related stigma as the lynchpin for tackling obesity: a comment on the contribution of the UK's policy response to obesity in the COVID-19 pandemic

In this paper, Jilly Gibson-Miller and co-author argue that the COVID-19 pandemic presents a unique opportunity to reshape the entrenched public discourse around obesity. This includes creating a new discourse that does not use stigmatising language and imagery; that does not frame obesity as a simple 'lifestyle choice' and that is informed by psychological evidence.

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Weight-related stigma is a serious public health issue. If, as the latest UK policy paper suggests, we are to 'Tackle obesity by empowering adults and children to live healthier lives' it is imperative that we face head-on the challenge of transforming the damaging narrative on obesity, in which a simple equation (*eat less, move more*) is applied to all individuals to achieve and maintain weight reduction. Way back in 2007, the Foresight report[1] brought attention to the myriad of bio-psycho-social influences that contribute to the development and maintenance of obesity (see Figure 1). Since then, experts have long since conceptualised obesity as a chronic, relapsing and multifaceted health condition; the language used to describe the condition has changed so that those living with obesity are not defined by their condition and 'lifestyle' is no longer considered directly synonymous with 'behaviour'.[2,3] This is in contrast to popular discourse on obesity, where words such as 'fat' and 'lazy' are still often used to describe the relationship between excess weight and personal characteristics and which still largely considers obesity to be a result of poor individual 'lifestyle' choices. This discourse has given rise to an incredibly negative and stigmatising narrative that leads to shaming and blaming people living with obesity. Experiencing weight-related stigma and discrimination is extremely damaging for people living with obesity and has detrimental physiological and psychological consequences, which have been found to actually *predict* weight gain.[4] As Health Psychologists, we are ever-mindful of the omission of the bio-psycho-social determinants of health in research, policy and practice; and the limited understanding of health and disease within a systems-based approach.[5] Promoting understanding of obesity in terms of the complex interplay between biological, psychological and sociological systems (to which we would now add a further layer of influence in the COVID-19 era, the socio-political context) is imperative for weight-related stigma to be challenged and changed. This would require everyone within the system to acknowledge, assimilate and act upon such complexity.

Promoting understanding of obesity in terms of the complex interplay between biological, psychological and sociological systems (to which we would now add a further layer of influence in the COVID-19 era, the socio-political context) is imperative for weight-related stigma to be challenged and changed

In the wake of the COVID-19 outbreak, a plethora of evidence strongly suggests that obesity is a key risk factor for COVID-19 complications, including hospitalisation and ventilation[6] and that people living with obesity are at greater risk of dying from COVID-19.[7] Those who fall into a classification of seriously overweight are advised to shield on health grounds.[8] Part of the response by

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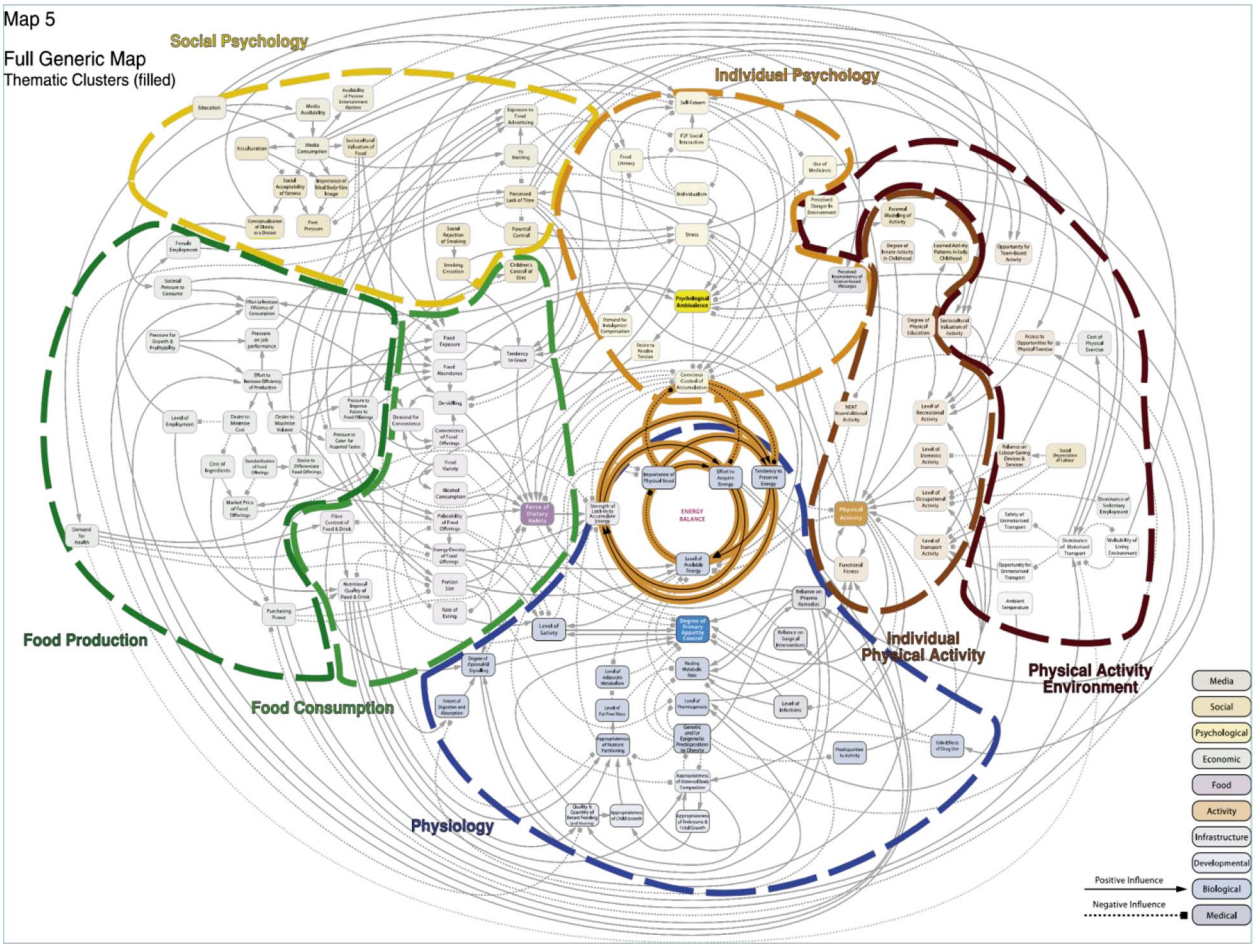
Figure 1. The Obesity Systems Map. Embracing complexity is the key to reducing stigma.the aftermath of COVID



the UK government has been the publication of a policy paper that launched a public health campaign focused on 'getting active and eating better' along with a restriction on food advertising.[9] Although this promotes a welcome (if long-overdue) renewal of dialogue in the public domain focused on obesity, there is a great risk of people living with obesity being stigmatised further if the perception remains that there is a simple link between COVID-19 and 'lifestyle' factors. The UK government has essentially called for people living with obesity to make a choice to lose weight by changing their lifestyle. Unchallenged, this ingrained belief is likely to create a blame culture that will increase stigma, increase shame around body weight (especially in those who are advised to shield), increase psychosocial distress, including mental health issues and disrupt weight management behaviour.

Weight-related stigma is pervasive across generations, societies, and cultures: as the world recovers from the COVID-19 pandemic, we believe this is a unique opportunity to reshape the entrenched public discourse around obesity. There is a need for urgent action to begin to create a worldwide culture change that instigates a new discourse about obesity that does not use stigmatising language and imagery, that does not frame obesity as a simple 'lifestyle choice' and that is informed by psychological evidence.[10] We reiterate the importance of taking action in relation to reducing stigma, outlined in recent expert reports[10,11] as a matter of priority, to shape government policy on tackling obesity. In the current context, it is clear that detailed information will be required by the government to guide the development of interventions that are innovative and responsive to the needs of people living with obesity in the aftermath of COVID-19. We call on the government to urgently fund

We call on the government to urgently fund researchers in the field to focus efforts on better understanding the unique stigma experiences of groups of different genders, cultures, religions and sexual orientations

researchers in the field to focus efforts on better understanding the unique stigma experiences of groups of different genders, cultures, religions and sexual orientations, as well as the additional impact of COVID-19 on these experiences. Weight stigma is unacceptable and it is imperative that people living with obesity are not stigmatised, and harmed further, as a result of the misrepresentation of the complex relationship between COVID-19 risk and obesity.

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COVID-19: the need to address health inequalities

Teresa Burdett and Anneyce Knight use this article to address some of the pertinent issues at present impacting health inequalities in our society which are being exacerbated by the Covid-19 pandemic. Strategies to combat the impact of Covid-19 in the population include Making Every Contact Count (MECC) and a tiered approach harnessing a variety of strategies across the population to reduce the devastating impact that Covid-19 is currently having in society.

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COVID-19 has rampaged throughout the UK with 4,115,509 cases and 120,580 deaths in the UK[1] and also a greater part of the world with 109,206,497 reported cases worldwide,[2] resulting in tragic loss of life and long-term ill health. However, while still trying to combat this pandemic, and provide quality of care to individuals requiring support who are fighting this pandemic disease and require long- and short-term rehabilitation afterwards, other questions have been raised. Nationally and internationally, answers are being sought to ensure that future strategies are effective in combating this potentially deadly disease.[3,4]

One of the most concerning implications of COVID-19 is that it appears to affect each section of the community unequally, including risks and outcomes. If you become very unwell with COVID-19 your chances of recovery depend not only upon effective treatment but also your age, as people over the age of 80 are 70 times more likely to die than 40 year olds.[5] Other factors have been identified including general health, long-term conditions, comorbidities and gender (more males die than females).[5,6] Furthermore, social determinants of health are also contributing factors, including socio-economic circumstances where the consequences of COVID-19 are higher for those living in the more deprived areas than those living in the least deprived.[5] Furthermore, the ethnic grouping you belong to is significant, as Black, Asian and minority ethnic individuals appear to be inversely affected by this condition. Death rates due to COVID-19 are the highest among individuals who belong to Black, Asian and minority ethnic groupings.[5,6] Regional inequalities are also evident in COVID-19 death rates, as rates in London are more than three times higher than in the South West region, which has the lowest rates:[5]

'*The scandal is not that the virus has disproportionately affected certain groups, but that it has taken a global pandemic to shine a light on deeply entrenched health inequalities*'.[7]

If you become very unwell with COVID-19 your chances of recovery depend not only upon effective treatment but also your age, as people over the age of 80 are 70 times more likely to die than 40 year olds.

As we seek to continue the battle against COVID-19, it is not only national and local policies that need to be reviewed; we will also need robust strategies and interventions and to work together with individuals and their communities at micro- and macro-levels. This means we will have to work constructively, collaboratively and creatively to enhance the health status of all members of the community.[8] This requires a person-centred and integrated approach that traverses all communities regardless of setting, socio-economic background, race and ethnicity.[9,10] This is to ensure that quality of life is improved for all and the health inequalities that COVID-19 has highlighted and may well perpetuate[11] are, in the short-term, reduced and, in the long-term, eradicated.[12] This is especially pertinent due to the demise of Public Health England and the lack of clarity around the health improvement role within the new National Institute for Health Protection.

A starting place, that can be used by all health and social care professionals,

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and indeed all individuals who have contact with the public within their daily interactions, is to expand the use of Making Every Contact Count (MECC) (Healthy Conversation Skills). MECC is a person-centred approach which seeks to address health inequalities relating to general health and long-term conditions. It is a model that enables brief opportunistic health interventions wherever people are whether they are patients, service-users, clients or customers, and it is already used by many healthcare professionals. It can easily be adapted to upskill not only all health and social care professionals but also community leaders, volunteers, faith leaders and the wider workforce (e.g. librarians) to have conversations to support and empower individuals post COVID and/or with long covid.[13] This upskilling of the wider workforce would increase the opportunities to reach the most vulnerable and 'at risk' groups who do not have access to health services. Empowering people using this health promotion tool can help people to change their health behaviours and is more effective than telling people what to do.[14] As an evidence-based model, it provides the basis for a brief conversation with individuals, or groups, where people can identify their own health and wellbeing needs and choose appropriate actions for them to work towards achieving their healthy goal.[13] It is an inclusive approach acknowledging everyone's individual circumstances and the wider social determinants of health.

MECC is a person-centred approach which seeks to address health inequalities relating to general health and long-term conditions

Alongside MECC, we need a tiered and comprehensive approach which includes long- and short-term goals to tackle the impact of COVID-19 which exacerbates existing health inequalities. These should be person-centred, community, governmental, integrative, national and global approaches.

CONFLICT OF INTEREST

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vaccines

MDPI

Systematic Review

Indian Biosimilars and Vaccines at Crossroads–Replicating the Success of Pharmagenerics

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Abstract: Background: The global pharma sector is fast shifting from generics to biologics and biosimilars with the first approval in Europe in 2006 followed by US approval in 2015. In the form of Hepatitis B vaccine, India saw its first recombinant biologics approval in 2000. Around 20% of generic medications and 62% of vaccines are now supplied by the Indian pharmaceutical industry. It is this good position in biologics and biosimilars production that could potentially improve healthcare via decreased treatment cost. India has witnessed large investments in biosimilars over the years. Numerous India-bred new players, e.g., Enzene Biosciences Ltd., are keen on biosimilars and have joined the race alongside the emerging giants, e.g., Biocon and Dr. Reddy's. A very positive sign was the remarkable disposition during the COVID-19 pandemic by Bharat Biotech and the Serum Institute of India. India's biopharmaceutical industry has been instrumental in producing and supplying preventives and therapeutics to fight COVID-19. Despite a weak supply chain and workforce pressure, the production was augmented to provide reasonably priced high-quality medications to more than 133 nations. Biosimilars could cost-effectively treat chronic diseases involving expensive conventional therapies, including diabetes, respiratory ailments, cancer, and connective tissue diseases. Biologics and biosimilars have been and are being tested to treat and manage COVID-19 symptoms characterized by inflammation and respiratory distress. Purpose of review: Although India boasts many universities, research centers, and a relatively skilled workforce, its global University–Industry collaboration ranking is 24, IPR ranking remains 47 and innovation ranking 39. This reveals a wide industry-academia gap to bridge. There are gaps in effective translational research in India that must be promptly and appropriately addressed. Innovation demands strong and effective collaborations among universities, techno-incubators, and industries. Methodology: Many successful research findings in academia do not get translation opportunities supposedly due to low industrial collaboration, low IP knowledge, and publication pressure with stringent timelines. In light of this, a detailed review of literature, including policy papers, government initiatives, and corporate reviews, was carried out, and the compilation and synthesis of the secondary data were meticulously summarized for the easy comprehension of the facts and roadmap ahead. For easy comprehension, charts, figures, and compiled tables are presented. Results: This review assesses India's situation in the biosimilar space, the gaps and areas to improve for Indian investment strategies, development, and innovation, addressing need for a more skilled workforce, industrial collaboration, and business models. Conclusions: This review also proposes forward an approach to empowering technopreneurs to develop MSMEs for large-scale operations to support India in taking innovative thoughts to the global level to ultimately realize a self-reliant India. The limitations of the compilation are also highlighted towards the end.

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1. Introduction

Due to the high cost of biologics, new legislation is introduced to encourage the development of biosimilars, which will increase treatment options, broaden access, and reduce costs. Biosimilars are structurally similar to their original biological molecule (originator; inspirer; reference product) but are not identical [1–3]. Nevertheless, their bioactivity is clinically very similar to the reference product in terms of safety and efficacy [4,5]. Their medication and function are similar to the original biologic at the same strength and dosage. Manufacturers of biosimilars could obtain commercial authorization to market them as biological drugs, being remarkably similar, after resolving the regulatory exclusivity and intellectual property issues for a biologic. There is an increasing demand for biologics and biosimilars particularly in treating auto-immune diseases and cancer (https://www.pfizer.com/news/articles/biologics_vs_biosimilars_key_differences_explained; 7 September 2022). The prevailing pandemic has severely dented healthcare and demanded vaccines, biologics, biosimilars, and generics to prevent or manage the symptoms.

There are a lot of competitions to develop, manufacture, market, and approve biologics and biosimilars globally. The COVID-19 pandemic demanded even monoclonal antibodies (mAbs), e.g., tocilizumab, sarilumab, and itolizumab, as therapeutics [6–9]. As a silver lining in the dark cloud, the pandemic has marked the turning point for Indian pharmaceuticals to put its best foot forward. The Indian government is encouraging domestic bioindustries to transform the crisis that COVID-19 poses into an opportunity to spread their wings in the biosimilar market. Indian vaccine stories shined well during the crisis period. New business models and approaches to develop indigenous vaccines, generics, and biosimilars were commendable. For instance, Zydus Cadila (a concern of Cadila healthcare) focused on interferon α-2b for commercialization as a biosimilar version for treatment (https://adisinsight.springer.com/drugs/800040283; 7 September 2022). Indian biopharma companies have shaped up the vaccine and biosimilar landscape with the entry of two additional Indian entities into the global marketplace during the pandemic. India also competes for global market positioning by adding strategies targeting the booming clinical trials and clinical research, increasing its skilled workforce, adopting innovative techniques in manufacturing, etc. Due to all this path-breaking, multipronged evolution, there is a need for revamping Indian regulatory standards for biosimilars approval.

The global demand for vaccines and biosimilars is on the rise, and therefore there is a huge market opportunity for biopharma business. A meticulous step-by-step plan for collaborations, assured prompt regulatory approval, and optimal market access for biosimilar research and commercialization are necessary—an indescribably complex endeavor. In face of the heightened competition from biosimilars, the businesses attempting to preserve the market share of branded biologic products are losing market focus. In order to maintain the momentum in the given circumstances, an integrated, strategic development and commercial plan from the very beginning of any biosimilar development programme could ensure the distinct competitiveness of biosimilars. This compilation intends to provide insights on the strengths, drawbacks, opportunities, and challenges of Indian biotech and biopharma companies as global players. The article discusses the history, scope, and evolution of biotechnology companies in India, methodologies, global vs. Indian biotech endeavors, market size and current scenario of Indian biotech companies in biopharma sector, healthcare scenario, translational research initiatives, prospects and bottlenecks, what ails Indian biotech going global, Indian vaccines in the global market, visionary perspectives, and ending with a conclusion. It emphasizes elevated Indian strategies and participation to lead and regulate the international biosimilars and vaccines market.

2. History, Scope and Evolution of Biotechnology Companies in India

Biotechnology is the development of products using biological systems (living organisms or their derivatives), including recombinants engineered from wild types to improve human life [10,11]. Its roots are in ancient processes that used animals, plants, and microorganisms to produce a variety of goods with economic benefits for humans. Modern biotechnology uses molecular-level genetic engineering to create transgenic (genetically modified) organisms that can be used to create vaccines, drugs, and diagnostic tools, among other things. Contrary to GM crops, which increase production to feed the world's population and produce biofuels for a cleaner environment, biopharmaceuticals, such as biologics and biosimilars, offer treatments for many fatal diseases which are critical for disease-free survival.

Therefore, the Indian government is aggressively promoting the development of the biotech sector due to its socioeconomic influence and potential for a sustainable future. India's bio-based industries are booming because of financial support from both the public and commercial sectors (such as angel investors and venture capitalists). Start-up grants, investments, and many other internal and external forms of financial support have been drawn to high-end innovative start-ups, particularly by recent Indian university graduates [12]. Indian bioindustry comprises of five broad divisions: biopharmaceuticals [13], agribiotech [14], bioinformatics [15], fermentation, and bio-based services. Producing medicines, diagnostics, and vaccinations (which are preventives) are all part of the biopharmaceutical industry. Of all bioindustries, the Indian biopharma sector is the one that generates the most income. The third-largest industry is agribiotech, which deals with transgenic plants, hybrid seeds, biofertilisers, biopesticides, etc. In the most recent period (2010–2011), agribiotech's revenue share climbed by 14%. Utilizing cells or cell derivatives, e.g., protein, natural amino acids, and yeast, bio fermentation (also known as white biotechnology) produces chemicals that are generally used in a B-to-B mode in the starch, refinery, liquor, materials, textile, and leather (tanning) sectors, to mention a few. Bio services, on the other hand, represent the only discernible bio industrial sector in India that deals with services, e.g., clinical trials, contract research, trading, etc., rather than necessarily involving a tangible product (https://www.indianmirror.com/indian-industries/biotechnology.html; https://www.birac.nic.in/; 7 September 2022) (Figure 1a,b).

Indian biotechnology and its industrial revolution present a significant historical legacy [16,17]. The Centre for Cellular and Molecular Biology (CCMB) set up by the Council of Scientific and Industrial Research (CSIR) was the first institution devoted to biotechnology in India in 1977. Subsequently, the National Institute of Immunology (NII) was founded by the Department of Science and Technology (DST) to support advanced biological research. The National Biotechnology Board (NBTB) was established in 1982 to promote scientific programmes in biotechnology and to strengthen indigenous capabilities. The NBTB was upgraded to an autonomous body in 1986 as the Department of Biotechnology (DBT) under the Ministry of Science and Technology who planned to promote and coordinate biotechnology programmes. DBT focused on improving scientific research both quantitatively and qualitatively, providing appropriate infrastructure, utilizing human resources, and promoting industry–academia collaborations [18,19]. The DBT developed the National Institute of Plant Genome Research (NIPGR), The Centre of DNA Fingerprinting and Diagnostics (CDFD), National Brain Research Institute (NBRI), Institute of Bioresources and Sustainable Development (IBSD), Institute of Life Sciences (ILS), Institute for Stem Cell Biology and Regenerative Medicine (INSTEM), National Agri-Food Biotechnology Institute (NABI), Translational Health Science and Technology Institute (THSTI), National Institute of Biomedical Genomics (NIBMG), etc. The DBT has also established biotechnology parks and bioincubators in various states, e.g., Uttar Pradesh (Lucknow), Karnataka (Bengaluru), Telangana (Hyderabad), Tamil Nadu (Chennai), Odisha (Bhubaneswar), Kerala, and Assam (https://dbtindia.gov.in/; https://dbtindia.gov.in/about-us/organization-structure/public-sector-undertaking, 7 September 2022). They are successfully accelerating the commercialization of new biobased

technologies, offering facilities to scientists, small and medium enterprises and promoting public-private partnerships. DBT established another autonomous unit, Biotechnology Industry Research Assistance Council (BIRAC), to promote innovation, empower emerging biotech start-ups, commercialize innovative discoveries, and promote industry–academia interactions [20].

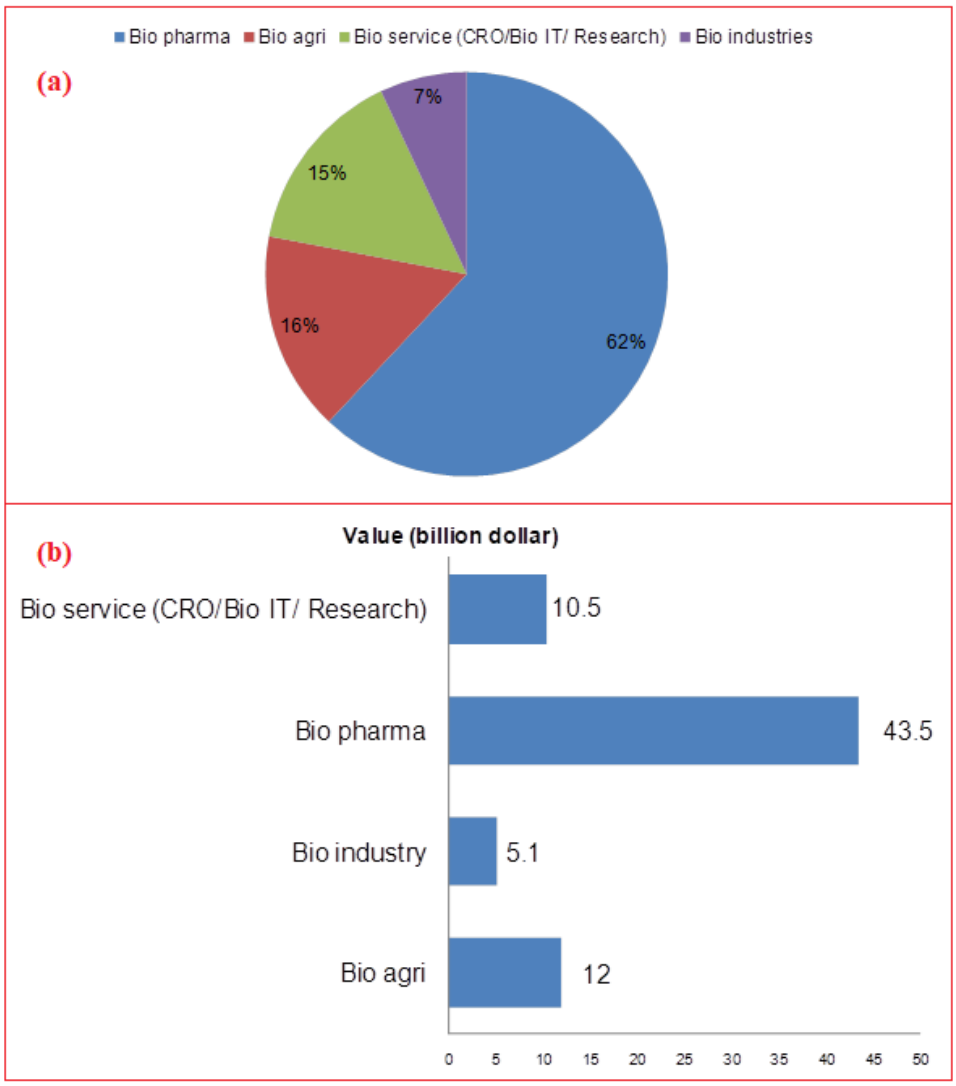

Figure 1. (**a**) Percent share of various biotechnology sector segments in India; (**b**) Contribution of different biotech sector segments towards Indian economy at 70.2 billion dollars in 2020 [13].

The foundation and growth of the Indian biotech industry is stimulated by different factors in the post-independence era [21]. Indian biotech ventures were established by various entrepreneurs working in Indian industrial set-ups and pharma industries, or academic scientists with industrial experience, or the home-coming of Indian scientists, post docs, and entrepreneurs, returning with vast industrial or academic experience. New biotech set-ups were founded by extending a division from the existing drug industry or diversifying a non-pharma company into a biotech start-up or established by multinational companies (Table 1). Government initiatives and innovative start-ups are involved in the generation of bio industries, involving diagnostics, bioinformatics, regenerative medicines, generics, vaccines, and biotherapeutics.

Table 1. The organic growth scenario of Indian bioindustries.

Triggering Factor	Beneficiary Organisation	Speciality Area	References
Scientists or local individual from various industrial sectors	XCyton Diagnostics (Bengaluru) GangaGen (Bengaluru) Shanta Biotechnics (Hyderabad)–now part of Sanofi Cytogenomics (Bengaluru) Bigtec (Bengaluru) Brilliant Bio Pharma Private Limited (Hyderabad)	Diagnostics Antimicrobials Biogenerics, diagnostics, contract research Bioinformatics Bioinformatics Veterinary Vaccines	[21]
Companies venturing into biotech	Serum Institute of India (Pune) Biocon (Bengaluru) Infosys (Bengaluru); Tata Consultancy Services (Mumbai) Zydus Cadila Bioogical E (Hyderabad) Intas Pharmaceuticals (Ahmedabad) Emcure–Gennova (Pune) Panacea Biotec (New Delhi) Wockhardt (Mumbai) Dr. Reddy's Laboratories (Hyderabad) GVK Biosciences (Hyderabad) Jubilant Biosys (Bengaluru)	Vaccines, biosimilars Generics, biologics, biosimilars Bioinformatics Generics, biologics, biosimilars Vaccines. Biologics Generics, biogenerics, contract manufacturing Biosimilars, Novel Vaccines Generics, vaccines Generics, biologics, vaccines Generics, vaccines, biosimilars, biologics Generics, biogenerics Bioinformatics, contract research	[21]
Academic scientist to bioentrepreneur	Bangalore Genei (Bengaluru) Avesthagen (Bengaluru) Strand Life Sciences (Bengaluru) Microtest Innovations (Bengaluru)	Reagents supply, contract research Plant biotech, diagnostics, nutraceuticals, contract research Bioinformatics Diagnostics	[21]
Industry professionals or academic scientists from overseas	Molecular Connections (Bengaluru); Cell Bhat Biotech (Bengaluru) Bharat Biotech International (Hyderabad) Genotypic Technologies (Bengaluru) Connexios Life Sciences (Bengaluru) Ocium Biosolutions, Mapmygenome (Hyderabad)	Bioinformatics, systems biology Diagnostics Vaccines, Biosimilars Bioinformatics, contract research Systems biology Bioinformatics, Diagnostics	[12,21]
Multinational company setting up in India	Quintiles India (Bengaluru); Accelrys (Bengaluru) Merck KGaA (Bengaluru); MWG (Bengaluru); Thermo-Fisher (Bengaluru); Sartorius (Bengaluru); DuPont (Hyderabad) GlaxoSmithKline Pharmaceuticals Ltd., Mumbai	Bioinformatics, contract research Reagents and equipment supply, customised bioservices; R&D facilities Generics, Vaccines	[21]
Govt. initiated biotech company	Indian Immunologicals (Hyderabad); Human Biological Institute (Ooty) Bharat Immunological and Biologicals Corporation Limited (BIBCOL), (Bulandsahar, UP) Indian Vaccine Corporation Limited (Delhi)	Vaccines (Animal and Human) Vaccines	-

Table 1. *Cont.*

Triggering Factor	Beneficiary Organisation	Speciality Area	References
Start-up as emerging biotech company	Med Genome (Bengaluru), X Code Life (Chennai), FARCAST Biosciences (Bengaluru)	Bioinformatics, Diagnostics, drug dicovery	-
	BUGWORKS (Bengaluru)	Antimicrobials	
	Pandorum (Bengaluru)	Tissue Engineering, Regenerative medicines	
	Oncostem Diagnostics (Bengaluru)	Diagnostics and therapy	
	Zumutor Biologics (Bengaluru)	Novel Immunotherapy and stem cell research.	

Bioindustry start-ups give India a place in the top 12 global destinations and 3rd place in Asia after China and Japan [22]. As per the Association of Biotechnology Led Enterprises (ABLE), the biotech sector will cross US $100 billion by 2025. With the biopharma sector having the largest share among the biotech set-up in India, it stands as the 3rd largest producer of pharmaceuticals globally and holds 14th rank by value (https://www.ibef.org/industry/pharmaceutical-india, 7 September 2022). While India has a stronghold in global market by supplying 40% of generics, more than 50% of global demand of vaccines is fulfilled by Indian pharma sector. The export of pharmaceuticals from India in the FY20 was US $16.3 billion. India's domestic pharmaceutical market turnover reached US $20.03 billion in 2019, a 9.8% increment from US $18.12 billion in 2018. The pharmaceutical export market turnover was US $24.4 billion in 2020–2021, witnessing an 18.1% (YoY) growth. India's domestic pharmaceutical market is estimated at US $41 billion in 2021, likely to grow to US $65 billion by 2024, and further expected to reach US $130 billion by 2030 (https://www.thehindu.com/brandhub/the-giant-leap-of-indias-pharmaceutical-industry/article65670866.ece, 7 September 2022).

The global pharma sector is fast shifting from generics to biologics and biosimilars. Biosimilars hold potential to improve patient's life by decreasing the treatment cost (https://www.gabionline.net/biosimilars/general, 7 September 2022). India is well placed in biologics and biosimilars production. Over the years, India has seen large investments in biosimilars [23]. Apart from Indian-bred indigenous companies, e.g., Biocon and Dr. Reddy's, who are currently the emerging giants, numerous new entities, e.g., Enzene Biosciences Ltd. (a subsidiary of Alkem Laboratories), are keen to produce biosimilars and have joined the race. Some of the other Indian biopharma giants have been briefly discussed in Supplementary Materials S1. The first approval of biosimilars was in 2006 in Europe, followed by the US in 2015. Since then, several biosimilars have been developed that are cost-effective and utilised across the globe to treat chronic diseases for their affordability and quality. They have also been used to treat non-infectious diseases, e.g., diabetes, respiratory problems, cancer, and connective tissue diseases, etc. India got its first approval for a Hepatitis B vaccine in 2000 [24]. The biosimilar guidelines were established in 2012 jointly by the Central Drug Standard Control Organisation (CDSCO) and the Department of Biotechnology (DBT). These guidelines on the production and approval of biosimilars were further revised in 2016. In 2019, India had 98 approved biosimilars. Currently, a couple of hundred active biosimilars are at various stages of research and development by several Indian biopharma industries [25].

3. Methodology

Data were sourced from the reports and publications available in the public domain, compiled, analyzed, and synthesized. Data were collected from authentic databases, e.g., Scopus, ScienceDirect, PubMed, Web-of-Science, and GoogleScholar, to name a few, information in the public domain (the websites) on several public and government health organizations and line departments, as well as policy making bodies. Numerous publicly available policy documents on the pharma companies' profile and several reference books

were also consulted. For critical in-depth coverage and compilation of the relevant contents, the key terms searched online included Indian biosimilars, Indian biopharmaceutical companies, growth of Indian bioindustries, biotech companies in the global biosimilars market, vaccine manufacturers, pharmagenerics, healthcare scenario, human resource inventories, etc. All the data thus obtained were carefully examined and only the closely matched reports/studies were considered for compilation and critical discussion while excluding the irrelevant or generalized reports. More than 300 reports and research documents were interpreted, 170 of which fulfilled the objective of the study and were discussed. All such documents have been duly cited and listed in the references section.

4. Global vs. Indian Biotech Endeavors

Research conducted by the Market line and DCAT on the global ranking of countries in terms of their biotechnological innovations states that the US is dominating with 48.2% in biotech market, 24% of the share is held by Asia-Pacific, followed by the Europe with 18.1%. The Middle East contributes 1.8% while the remaining 7.9% of the market is captured by the rest of the world. India carries 3% of share in the global market and is placed at 52nd position in global ranking (https://birac.nic.in/big.php, 7 September 2022). Further, India is the pioneer in the worldwide supply of DPT, BCG, and measles vaccines. Biotechnology has the potential to drive India's economy to USD 5 Trillion by 2024. The US and the European Union are leading in this sector [26]. The US is at the leading position followed by Japan with respect to R&D expenditure in the biopharmaceutical space. Other countries, e.g., Switzerland, Germany, France, and Denmark, also significantly increased their investment in R&D in the recent past. China boosted its R&D expenses by 9.1% from 2014 to 2018 (https://www.gabionline.net/biosimilars/general, 7 September 2022). As indicated by a report of the Organization for Economic Cooperation and Development (OECD) on science and innovation (2010), the business picture has also improved for a few non-OECD nations, including Brazil, India, China, Singapore, and South Africa [27].

Europe is leading in terms of global production and commercialization of biosimilars, followed by Asia-Pacific nations which include countries, such as South Korea, Japan, India, and China [28]. While Korea contributes 43% to the global biosimilars market, the Indian biopharma sector is large and is in the most advanced stage to lead the biosimilars market in the Asia-Pacific. The global biosimilar market is expected to reach US $35.7 billion by 2025 from the current US $11.8 billion (2020) and expected to grow at a CAGR of 24.7% [27].

A list of manufactured biosimilars have also been provided to understand how other countries have fared in the biosimilars market capture (Table 2) along with Indian biosimilars that have been provided in Table 3. India launched its first rituximab biosimilar Reditux by Dr. Reddy's Laboratories. The world's first adalimumab biosimilar Exemptia was manufactured and marketed by Zydus Cadila in India [29]. CANMab, the world's first biosimilar version of Herceptin, developed collaboratively by Biocon and Mylan [30], was introduced in India in Feb 2014. Biocon launched a biosimilar Glargine Insulin in 2016, and successfully marketed the same in Japan. Biocon and Mylan as global partners developed Ogivri, Trastuzumab, and Fulphila (Pegfilgrastim), which have received US FDA approval [24]. All these achievements speak highly to how India has made its name in the biosimilars market with respect to the other countries.

Table 2. Dominant biotech companies in global biosimilars market with market share of the US and others, except India.

Industry	Country	Flagship Biosimilar	Market Share
Johnson and Johnson	USA	Remicade (Infliximab) [31]	48.2%
Pfizer	USA	Inflectra®®® (infliximab-dyyb in the US) [32]	
Mylan	USA	Ogivri (Trastuzumab) [33]	
Biogen	USA	Byooviz [34]	
Eli Lilly	USA	Insulin Glargine [35]	
Coherus Bioscience	USA	Cimerli (Ranibizumab-eqrn) [36–38]	
MSD (Merck & Co)	Germany	Ontruzant (Trastuzumab) [39]	18.1%
Boehringer Ingelheim	Germany	Cyltezo (adalimumab-adbm) [40]	
Fresenius Kabi AG	Germany	Stimufend [41]	
StadaArzneimittel AG	Germany	Silapo (epoetin-zeta) [42]	
mABxience	Switzerland	Novex (rituximab) [43]	
Roche	Switzerland	Lucentis (ranibizumab) [44]	
Sanofi Aventis	France	Lovenox (enoxaparin sodium) [45]	
GlaxoSmithKline	British	Nucala (mepolizumab) [46]	
Teva Pharmaceutical	Israel	Truxima (rituximab-abbs) [47]	
Gan and Lee Pharmaceuticals	China	Glargine [48]	
Amega Biotech	Argentina	Neutropine (Filgrastim) [49]	
Samsung Biologics	South Korea	Byooviz [34]	
Celltrion	South Korea	Remsima [50]	
Chong Kun Dang	South Korea	Darbepoetin Alfa [51]	
Probiomed	Mexico	Trastuzumab [52,53]	
Apotex	Canada	Apobiologix (pegfilgrastim) [54]	
JCR Pharmaceuticals	Japan	Agalsidase beta [55]	
Gedeon Richter	Hungary	Terrosa [56]	
Biocad	Russia	Trastuzumab [57]	

Table 3. A list of the approved Indian biosimilars which accounts for only 3% of global share.

Product	Company Name	Active Drug Molecule	Therapeutic Use in
Glaritus	Wockhardt	Insulin Glargine	Diabetes
Grafeel	Dr. Reddy's Laboratories	Filgrastin	Neutropenia
Pegfilgrastism	Lupin	Pegfilgrastin	Cancer, Neutropenia
Epofer	Emcure	Epoetin alpha	Anemia
Zyrop	Cadila Healthcare	Erythropeotin	Chronic kidney failure
Krabeva	Biocon	Bevacizumab	Colorectal cancer
Bevacirel	Reliance Life Sciences		
Cizumab	Hetero		
Erbitux		Cetuximab	Colorectal cancer
Acellbia	Biocad	Rituximab	NonHodgkin Lymphoma
Maball	Hetero Group		
maTabs	Intas Pharmaceuticals		
Adafrar	Torrent Pharmaceuticals	Adalimumab	Rheumatoid Athritis, Crohn's disease
CaNMab	Biocon	Transtuzumab	Breast cancer
Intacept	Intas Pharmaceuticals	Entanercept	Rheumatoid Athritis
Relibeta	Reliance Life Sciences	Interferon Beta 1a	Multiple sclerosis
Razumab	Intas Pharmaceuticals	Ranibizumab	Degenerative myopia
AbcixiRel	Reliance Life Sciences	Abciximab	Angina, Cardiac ischemia
Basalog	Biocon	insulin glargine	Diabetes
Biovac-B	Wockhardt	hepatitis B vaccine	Hepatitis B
FostiRel	Reliance Life Sciences	follitropin beta	Female infertility
Mirel	Reliance Life Sciences	reteplase	Myocardial Infraction
Zavinex	Cadila Health Care	Interferon alfa-2b	Chronic hepatitis B and C
Choriorel	Reliance Life Sciences	chorionic gonadotrophin hormone r-hCG	Female infertility

5. Market size and Current Scenario of Indian Biotech Companies in Biopharma Sector

Bioindustry has offered boost to the Indian economy. There are more than 2500 Indian biotechnology companies and more than 2700 start-ups. Indian bioindustry was worth US $63 billion in 2019, and is projected to be US $102 billion by 2025, with a CAGR of 10.9%. During this period, it is expected to spike by 19% from the current 3% of global market share. Biopharmaceuticals alone contributed about 62% in 2020, trailing 16% behind bioagriculture and 15% behind bioservices [58,59]. The sector is growing and becoming a leading clinical trial, contract research, and manufacturing destination. The Indian pharma sector inclines towards research and production of particularly biosimilars and biologics. Research works in India on biosimilars may provide promising cost-effective therapeutic solutions especially during recent times when the globe is dealing with recovery from the COVID-19 pandemic. The major current players in the Indian biosimilars market are briefly described in Supplementary Material file.

India is the second worst hit country in terms of health and economics by the recent COVID-19 pandemic, affecting various sectors, e.g., food, agriculture, aviation, and tourism, because of which the GDP has caved in [60–62]. The Indian pharmaceutical industry struggled because of the bans imposed on the import/export of a few crucial drugs, equipment, and PPE kit. However, the '*Atmanirbhar Bharat*' (Self-reliant India) initiative offered great incentive in enhancing economic activities. Poor accessibility to raw materials due to a disrupted supply chain made it harder to meet the increasing demand for drugs. Despite the economic crises, labor shortage, and logistics crisis, the Indian pharma industry has raised hope and is constantly pursuing the development of generic drugs and vaccines (Table 4). The country is currently dominating the global generics market with a size of US $55 billion. Covishield, being manufactured by the Serum Institute of India, was developed jointly by Astrazeneca and Oxford University. Covaxin is the first indigenous vaccine by Bharat Biotech Ltd. in collaboration with the Indian council of Medical Research (ICMR) and the National Institute of Virology (NIV). Both the vaccines have been approved for 'emergency use' by the Drug Controller General of India (DCGI). Other vaccines either received emergency authorization or remain under different phases of clinical trials, as detailed in Table 5.

Table 4. List of some Indian government, public sector undertaking and private sector vaccine manufacturers.

Sl. No.	Manufacturer	Licensed Vaccine	Target Species	Reference
1.	BCG Vaccine Laboratory, Guindy, Tamilnadu, India.	Tuberculine, BCG	Human	[63,64]
2.	Pasteur Institute of India, Coonoor, The Nilgiris, Tamilnadu, India.	DTP, DT, TT and inactivated rabies vaccine	Humans and canine	[64–66]
3.	Central Research Institute, Kasauli, Solan, Himachal Pradesh, India.	Yellow fever, JE, DTP, DT, TT	Humans	[64,67]
4.	BIBCOL, Chola, Uttar Pradesh, India.	bOPV	Human	[64,68]
5.	Haffkine, Parle, Mumbai, India.	bOPVand mOPV	Human	[68]
6.	Human biological Institute, a division of Indian Immunologicals Limited, Hyderabad, Telangana, India.	Rabies, DTP, TT, DT, Hep- B, Pentavalent (DTP+Hib+HepB)	Human and canine	[64,68]
7.	HLL Biotech Ltd., Taramani, Chennai, Tamil Nadu, India.	Hep B, DTwP- HepB-Hib	Human	[68]

Table 4. *Cont.*

Sl. No.	Manufacturer	Licensed Vaccine	Target Species	Reference
8.	Bharat biotech International Ltd., Hyderabad, Telangana, India.	Hib, Rabies, bOPV, mOPV, DTP+Hib+HepB, Vi polysaccharide Typhoid, H1N1, DTP, DTP+HepB, Rotavirus vaccine, Inactivated JE vaccine, Typhoid+TT Conjugate Vaccine andDTP+Hep- B+Hib (Liquid), DTP+Hib, BBV152 Covaxin	Human, canine	[64,68]
9.	Biological E, Hyderabad, Andhra Pradesh, India.	DTP, TT, JE bulk & DT	Humans	[64,67]
10.	Biomed Pvt. Ltd., Ghaziabad, Uttar Pradesh, India.	Hib, Meningococcal Polysaccharide, bOPV, Rabies, Meningococcal polysaccharide.		
11.	Cadila Healthcare, Ahmedabad, Gujarat, India.	Rabies, H1N1, trivalent influenza	Human	[64,68]
12.	Serum Institute of India, Pune, Maharastra, India.	DTP, TT, DT, Hep-B, Hib, MMR, Measles, Rubella, BCG, IPV, DTP+HepB+Hib (Liquid+lyophilised), DTP+HepB, DTP+Hib, H1N1, Meningococcal A conjugate (lyophilised), Mumps, MR, H1N1(whole virion inactivated), Measles+Mumps, Measles+Rubela, Seasonal Influenza vaccine, COVID-19 vaccine	Human	[64,67,68]
13.	Shantha Biotechnics Ltd., Hyderabad, India.	DTP, DTP+HepB+Hib (Liquid), DTP+Hib, DPT+Hep B, TT, Hib, Hep-B, DT bulk, TT Bulk, Hib Bulk, Hep B Bulk, DTP bulk, DTP+HepB+Hib bulk, DTP+HepB+Hib RTF bulk, Oral cholera vaccine, IPV RTF Bulk, IPV	Human	[64,67,68]

Various biologics and biosimilars have been tested and are under trial to treat and manage COVID-19 symptoms characterized by inflammation and respiratory distress, e.g., Celltrion Healthcare's infliximab biosimilar, Remsima, to control cytokine release syndrome mediated immune response in COVID-19, and Bevacizumab, to treat pulmonary oedema related acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Tocilizumab, an anti–IL-6 receptor monoclonal antibody (mAb) has been proven to treat COVID-19 by reducing inflammation and maintaining blood pressure levels. Eculizumab and Ravulizumab are under clinical trials to treat moderate to severe pneumonia-associated COVID-19. Itolizumab developed by Biocon biologics is also used to treat chronic respiratory syndrome (CRS) in COVID-19 patients, approved for emergency use by Indian regulatory authorities. Pfizer evaluating a biologic tofacitinib to treat inflammation, and Zydus Cadila is investigating on the efficacy of Interferon α-2b to treat COVID-19 [69,70]. Apart from the already established pharma and biopharma giants, the Indian government along with DBT and other foreign collaborators such as the World Bank are working on providing various grants and funding schemes to bridge the gap between industry and academia, as detailed in Supplementary Materials S2.

Table 5. Various Indian biopharmaceutical companies engaged in COVID-19 vaccines development and manufacturing (https://covid19.trackvaccines.org/country/india/, 9 October 2022).

Vaccines	Indian Manufacturer	Collaborator(s)	Current Regulatory Status
Covishield	Serum Institute of India, Pune, India	Oxford-AstraZeneca	Approved
Covaxin	BharatBiotech Int. Ltd., Hyderabad, India	Indian Council of Medical Research, National Institute of Virology	Approved
ZyCov-D	Cadila Healthcare Ltd., Ahmedabad, India	Department of Biotechnology, India	Approved
Sputinik V	Dr. Reddy's lab, Hyderabad, India	Gamaleya National Centre, Russia	Approved
NCV-COV2373	Serum Institute of India, Pune	Novovax	Emergency authorisation
HGCO 19 m-RNA based vaccine	Genova, Pune, India	HDT-Bio, US	Approved
Recombinant protein-based Vaccine (Corbevax)	Biological E, Hyderabad, India	DBT Baylor College, US	Approved
Codon-deoptimised live attenuated COVID-19 Vaccine	Indian Immunologicals Limited, India	Griffith University, Australia	Pre-clinical
Warm COVID-19 Vaccine	Mynvax, Indian institute of Science, Bengaluru, India	BIRAC	

6. Healthcare Scenario, Translational Research—Initiatives, Prospects and Bottlenecks

Translational research is an interdependent lab-to-land or bed to bench scale process by which the findings of basic research are translated into economically feasible applications to improve or solve problems in healthcare, ecology and ecosystem, and other identified sectors. Translational research ensures progress in basic scientific research and the application of the scientific understanding and technological advancements for economic benefits. Translational research has two phases, T1: basic science discoveries utilized to develop novel processes or product, and T2: clinical research focusing on improving the existing clinical practices [71,72]. Having witnessed a great rise as a key global player in generic pharmaceuticals, it is observed that baring a few instances here-and-there India faces various challenges in the research and development of novel clinical interventions, especially on account of serious long-term sustainable collaborations with the key global players. This is slowly but steadily eroding the much-awaited organic growth in this promising sector with strong economic potential.

The Indian government through DBT under the Ministry of Science and Technology, has taken several initiatives to promote translational research in India. The first initiative was to establish an autonomous institution 'Translational Health Science and Technology Institute' in 2010. The focus of the organization is to develop novel strategies for the diagnosis and management of diseases by promoting innovative healthcare through multidisciplinary approach through inter-institutional and industry–academia collaborations to promote translational research.

The Stanford-India Biodesign (SIB) programme was started under its aegis in 2007 and continued till 2014. SIB was an innovation programme implemented by Stanford University, DBT, All India Institute of Medical Sciences (AIIMS), New Delhi, and Indian Institute of Technology, Delhi (IITD), in collaboration with Queensland University of Technology, Australia and Hiroshima University, Japan. The objective was to train the medical technology innovators in India to innovate processes and products that are affordable and accessible to the Indian population. The programme trained more than 100 medical technology innovators and entrepreneurs, more than 50 prototypes were developed, and more than 50 medical devices were developed by the young innovators. Of these, 15 technologies have been translated successfully, including five medical devices, and 11 start-ups became sustainable [73].

National Pharma mission through the 'Make in India' campaign had also empowered start-ups, enterprises, and increased industry-academia collaborations. The Central Drug Standard Control Organization (CDSCO), India, is also trying to reform the rules for approval process for novel drugs, new interventions, and new medical devices as per the prevailing requirements [73].

The goal of translational research is doing work in this biotech sector. However, there are certain roadblocks, bottlenecks, and issues at various levels, primarily societal, cultural, and regulatory. The first and important challenge is the difference of approach between the clinicians and the general scientists. The differences lead to a lack of communication, training, and education, and thereby varied views on the research and development outcomes. The other critical factor could be the cultural difference between the nations. The lack of appropriate scientific infrastructure, resources and workforce also is a critical barrier for translational research. The next important factor is the complex regulatory environment and ethical issues, including intellectual property rights, cell/tissue banking, sample transfer regulations, toxicology (safety issues), product manufacturing regulations, approval process for the product before hitting the market, clinical trials, etc. [74].

Another important issue in translational research is related to funding and incentives provided to research scientists. Governmental funding mechanism is time-consuming to obtain and non-transparent. The review process for a grant is longer, and the tracking of grants is not accessible. The communication process from reviewer to investigator is not clear. These kinds of issues need attention to improve the culture of scientific research and its output. Scientists, clinical researchers, and academicians are demanding a transparent, duplication-free, improved Indian grant framework. A common online portal for grant applications will reduce the time for grant revision, maintenance of transparency, and decrease the duplication of scientific objectives. Some researchers are also pointing towards a lack of incentives and rewards to researchers. A thorough review process should be implicated, and merit-based award systems must be created to provide support and encouragement to the scientific community. These funding agencies should have both academic and industrial experts for the neat examination of research objectives with translational potential. Another important solution to improve Indian research funding is to build a national mission mode involving public bodies, different trusts, and private institutes [75].

7. What Ails Indian Biotech Going Global?

The notion that developing nations are, at best, good service providers and lack the infrastructure to participate in cutting-edge technology to innovate products appears to have greatly hindered India's organic growth as compared to that of many other otherwise successful nations. This entails implementing novel approaches or methods to deal with diverse societal concerns. After the United States and China, India has the third-highest number of start-ups. Entrepreneurship-based organizations place an undue emphasis on customer acquisition at the expense of long-term revenue generation plans. In the upcoming sections below, we've attempted to highlight some of the potential reasons why the Indian biotech industry is struggling to expand internationally. The same is represented below as a SWOT analysis.

7.1. SWOT Analysis of Indian Biotechnology Industry in General and Biosimilars in Particular

As discussed, biosimilars represent the generic version of biologic products that could reduce healthcare costs. These innovated biological compounds exhibit similar efficacy and safety levels as their reference products. Thus, it provides wide-spectrum and cost-effective access to life-saving medications. However, considering the scale of operations at stake, a critical understanding of the state-of-the-art of the Indian biotech sector in general and the biosimilar industry in particular, considering the strengths, weaknesses, opportunities, and threats, is necessary. It is noteworthy that the strengths and weaknesses are the internalized factors of the biosimilar industry ecosystem and opportunities and

threats are the externalized factors. Similarly, strengths and opportunities together would facilitate an organic growth to the sector while weaknesses and threats would drag the growth prospects (Figure 2).

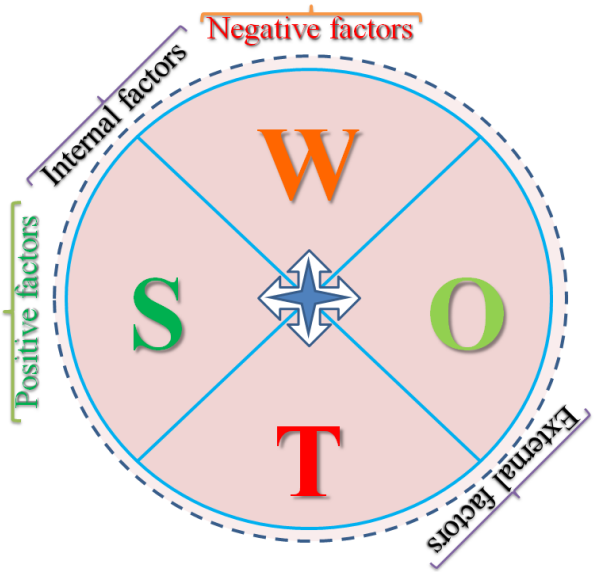

Figure 2. The SWOT chart depicting the interrelationship and correlation of growth parameters that affect a corporate ecosystem.

Table 6 outlines the factors that could either positively or negatively impact the growth prospects of the Indian biosimilars and vaccines industry, which is at a crossroads in its quest to replicate the success of pharmagenerics.

7.2. Lack of Innovation

Although the culture of entrepreneurship has been hitting hard, start-ups invariably lack innovation and have weak business models, focusing primarily on the predictable imitative business models and not venturing into high financial risk. The number of patents filed by India is very low, and only 7% of them are filed by the start-ups. The reasons for the lack of innovation in business model are poor development, less translation-oriented education, fear of failure, and funding issues [76]. Innovation depends upon resourceful human capital, investments, business environment, and performance enablers. The government of India should establish dedicated institutions, universities, and centers of excellence to provide education on the issues pertaining innovations in SMEs to improve and promote the culture of innovation. Investments for SMEs should be continual from government and market sectors to meet the demands. Low interest loans should be provided by the banks for setting up innovative ideas. Setting up collaborations between SME clusters and government to create value across the value chain, innovators must discuss with experts and consultants to understand the consumer demands and market trends. Mindset and cultural aspect also play a major role in entrepreneurship in India. Innovators should understand that frugal engineering is not the task to improve but rather to implicate in solving the risk–reward equation for entrepreneurship in India. Indian biopharma companies are now at the early stage of innovative policies. Such innovators are working in local and international collaboration among research institutes, health organizations, universities, and Indian or foreign based firms to adopt new technologies and business policies [77].

Table 6. Growth prospects of Indian biosimilars and vaccines industry: factors either contributing positively or affecting negatively.

	Positively Contributing Factors	Negatively Affecting Factors
Internal factors	Strengths (S) 1. Young and aspiring workforce 2. Cost competitiveness 3. High efficacy, low cost and akin safety level; growing demand in healthcare 4. Affordable, low-cost biosimilars make medication cost-effective in a price-sensitive Indian market 5. Reduced cycle in synthesis and regulatory compliance compared to innovator molecule 6. Innovation, R&D focus in innovative therapeutics as key player at global scale 7. Government regulatory assistance to produce biosimilars 8. Government initiatives to foster confidence and encourage investment	Weaknesses (W) 1. Poor Industry-Academia alliance 2. Low government funding to industry 3. Complex regulatory compliance process; lack of confidence in regulatory bodies and policy makers leading to high corporate cost in approval 4. Physicians not prescribing biosimilars; low awareness among the doctor and patient 5. Higher price compared to conventional generic drugs 6. Pharmacovigilance to monitor efficacy and safety needed for possible immunogenicity 7. Altered production process may alter biosimilars' property 8. Batch-wise uniform production is a challenge; needs skilled manpower, and validated and verifiable SOP
External factors	Opportunities (O) 1. Green-field, favourable emerging global biosimilars market 2. Fast-growing biopharma trade; US $300 million Indian biosimilar market anticipated to be worth US $40 billion by 2030 3. Over next few years, patent protection of many biologics expire 4. Vast prospect for cost-effective Indian biosimilars; biologics company start-ups booming 5. Biosimilar to cost 20–30% less than biologicals; low cost makes it affordable and accessible as demand grows 6. Government pledges to fund up to US $1.3 billion on API-based pharma business 7. Making APIs locally appear doable in next couple of years; to drive developing biotech-based medicines in India for the world 8. Efforts of DBT and BIRAC to support Indian biotech industry would benefit biologics industry 9. Government strategies focus on globally-acceptable legislation, entrepreneurship, industry-academia and public-private partnerships, and investment avenues for business house, investor and other agencies	Threats (T) 1. Stronger Chinese and Korean influence 2. Bargaining power of Indian companies with international patent litigations; patent litigation stifles smaller company from getting into biosimilars business 3. Lack of a comprehensive regulatory framework for biosimilars development 4. Tough approval process for pharama companies to enter global market 5. Delay in clinical trials approval, new pharma pricing policy, uniform code for sales and marketing practises, compulsory licencing, product quality, regularity uncertainty, reluctant to prescribe, and production complexity 6. Substantial competition from branded biologics than the tough competition as posed by small-molecule generics

7.3. Lack of Ventures

India lacks sufficient funding compared to the west for translational research. It depends largely on venture/angel funding. Due to high risk and challenging journey of innovative research, investors have reservations in supporting a start-up. The number of investors from private sectors coming forward as funders is very low. Indian government, thus, is the primary investor for start-ups [78]. However, it spends only 0.7% of its GDP in research and development while China spends 2.19%, Japan around 3.9%, South Korea spends 4.81%, and Israel spends 4.95% of its GDP in the R&D sector [79]. India is depending on overseas investors, basically from North America, Europe, Japan, and China. There is a lack of participation by domestic investors due to insufficient funds and a lack of risk-taking attitude. Another reason could be due to the regulatory environment. The difference in venture tax rates between publicly listed and private listed start-ups is discouraging the

angel funding from India. Private investors and especially public banks are not interested in investing or lending commercial loans due to debt overhang in a large number of private firms [80]. Although case-specific funding from the government is appreciable, it covers only seed capital and a meagre risk capital. After proof-of-concept stage, the start-ups need accelerator funding for the commercialization stage. The commercialization of biotechnology products is longer, costlier, and risky primarily due to the legal and ethical challenges, which Indian society is typically averse to. Further, venture capitalists do not find investing in biotechnology attractive as there is no smart exit route for them. They may be more willing to make the investment if they can get a return through the IPO (stock market) [81]. However, there is a silver lining: amidst economic crises due to the recent pandemic, the year 2020 saw a five-fold increase in venture funding to the pharmaceutical sector compared to just the previous year.

7.4. Loose Ignition Grant System

Government funding for young professionals in India to develop through ignition grants has been respectable in recent years. However, it is urgently necessary for other sources to take comparable actions. Although there are several programmes for government support, the procedure is drawn out, requires a ton of paperwork, and requires administrative work that is out of step with the idea of 'ease of doing business'. Additionally, it appears that the examination of a grant request is ineffective due to insufficient communication with the principal investigator. A grant proposal's duration from submission to final approval is agonizingly protracted [82–84]. The cash bottleneck with the Indian funding agencies appears to be serious, even after technical approval, financial evaluation, and funding. Despite a rigorous assessment, the grant is accepted, but scientists do not get the money in a timely manner, which affects their long-term career prospects, their ambition, and motivation. Young biotechnology professionals lose momentum when they do not receive opportunities and incentives in a timely manner. It is essential to concentrate on large-scale collaboration networks, including several institutions and research groups with interdisciplinary perspectives, that could draw both local and foreign financing systems and enhance innovation [85].

7.5. Lack of Leadership Vision

A clear vision and good leadership are essential components that support the creation and maintenance of collaborations for the systemic, natural expansion of any organization. It is important to note that strong partnerships and long-term collaborations between businesses, institutions of higher learning, governmental organizations, and researchers are on the horizon, particularly in the biopharma industry. The creation of a start-up ecosystem is hampered by visionless leadership and assistance focused on skilled labor. As a result, 50% of start-up enterprises fail to secure funding due to a lack of capable and devoted leadership [86,87]. New businesses fail or have delayed growth because of a lack of leadership. Failures are mostly caused by the absence of long-term company objectives, the absence of creative ideas, and the slow acceptance of new business models and markets. Poor management and communication abilities also affect networking and fund-raising efforts. A start-up's ability to scale up and grow generally is impacted by collaboration issues. According to the MSME, there are 6.33 crore small, medium, and micro-enterprises in India, with 90% of them being micro-enterprises. The workforce is mostly engaged in product manufacture, marketing, and financial management in these small and micro-enterprises. However, innovative plans to upgrade and expand the business are low. Indian entrepreneurs need to be trained to effectively manage marketing, communication, and working capital to get a holistic view on how to run a business in this kind of domain [88].

7.6. Quality Human Resource

The lack of a competent skilled human resource is another major concern for a start-up. *Aspiring Minds* magazine reports that only 3.84% of graduates have the basic technical and analytical skill sets needed for a start-up.

To enhance their capabilities and improve their global competitiveness, Indian companies would need highly trained personnel. Many highly skilled research scientists and PhDs migrate abroad for better financial support for their research and self. India needs to train the graduates and provide them strong research infrastructure to hone their skills for improved quality human resource that don't migrate and supports the local ecosystem [89]. Although Indian R&D has produced a sizable scientific workforce, very few scientific leaders and very few ideas have achieved commercial success. To create a high-value knowledge economy, universities should encourage interdisciplinary research. An Indian researcher typically comes up with solutions to research problems without considering any potential applications for industry. Success depends on carefully considering every step of the innovation's journey from the research lab to the patient's bedside. To 'close the loop', the way such challenges are approached must alter, and study findings must consider their commercial viability. Universities and research institutions should employ personnel with expertise in intellectual property (IP) and technology transfer. Academicians and researchers should work together with industry to license their inventions and promote the results of their study. A more robust framework of industry–academia partnership might lead to the development of technological commercialization techniques, which would advance social development and the economy. The redesign of a research-based curriculum emphasizing the enhancement of a domain-specific skill set, more vocational hands-on trainings, improved publishing practices, faculty enrichment programmes, student exchange programmes, merit-based incentives, and awards for researchers and promoting research institute, university, and industry collaboration are just a few Indian research areas that need improvement to match the global arena [90].

7.7. Status of Industry-Academia Partnering

Although India boasts many universities, research centers, and a relatively skilled workforce, the global university–industry collaboration ranking of India is 24, the IPR ranking is 47, and innovation ranking is 39. This reveals a seemingly wide industry–academia gap that needs to be bridged. Many successful research findings in academia, even though promising, may not translate to novel commercialized technologies or patents. They are not getting the opportunities due to a lack of industrial collaborations, lack of IP knowledge, and due to the practices of multiple publications in stringent timelines [91–96].

India may be inspired by Israel biotechnology momentum [97]. The Israeli government supports many programmes that have improved the biotechnology sector through innovation and skill development in biotechnology in general and medical research. The funding for life science research is half of its total research funding. The government supports start-ups after a proof of feasibility phase to success, which is crucial for the start-up's survival. Israel's high-tech incubators are public-private partnership ventures, nurturing young biotech companies by offering R&D facilities, experienced management, as well as financial and administrative support. The Magnet framework, a consortium of industries and research institutions to develop innovative technology, was established by the Israeli government for this. Academic research groups are engaged in scientific or technological research to promote applied research and commercialize the technologies as per industry need. Then, manufacturing companies develop competitive and innovative products. 'Magnet' also supports high-tech incubators providing a home for innovative project development. It provides long-term financial support with exemption of royalties to industries, promoting a solid framework for ground-breaking innovations. Bioplan 2000 supports biotech incubators through funding, providing infrastructure and management. Along with this, the Ministry of Science, Culture and Sport has supported biotechnology as 'national programme', where various research groups were involved

in developing the skills and improving infrastructure and fund allocation for academic biotechnology and medical research. Israel's leading biotech companies are built on academic excellence, an enabled workforce, entrepreneurial endeavor, high-end technologies, extraordinary funding support, and skilled management [98].

Indian government slowly though surely has been taking several steps to build an industry-academia collaboration ecosystem. A dedicated 'Entrepreneurship and Skill Development' Ministry has been recently established to promote young professionals for entrepreneurship and to train the manpower as per the industry need. Atal innovation mission intends to establish Technology Business Incubators (TBIs) in universities. The National Initiative for Developing and Harnessing Innovations (NIDHI), Promoting Innovations in Individuals, Start-ups and MSMEs (PRISM), Impacting Research, Innovation and Technology (IMPRINT) are few other programmes for industry–academia collaboration. The National Biopharma Mission 'Innovate in India' is a mission for industry–academia collaborations established by Department of Biotechnology (DBT) in collaboration with the World Bank. The program is devoted to technological and product development in the biopharmaceutical sector to enable stakeholders to become globally competitive. This specifically focused on the development of vaccine, biosimilars, therapeutics, and diagnostics. Additionally, there are several fellowships, e.g., the Prime Minister Fellowship, Department of Science and Technology (DST), and CSIR-Industry sponsored research scheme initiative, from the government to strengthen innovation and contribute to national economy through industry–academia links [99,100].

7.8. Mindset Issues—Need to Embrace the State-of-Art Technologies

Biopharma-related legal experts opine that although India's domestic biosimilar market is rising, its international business may be impeded due to a loose regulatory structure that makes other nations wary of the quality of the biosimilars. There are 98 approved biosimilars in India, with at least 50 on the market—the most of any country. In comparison, according to a WHO survey, the US has 26 approved biosimilars and the European Union has 61 [101]. The heart of the operation is bioprocess technology that has developed significantly in last decades. State-of-the-art techno-management approaches, e.g., quality by design (QbD), process analytical technology (PAT), single use technology, just-in-time, or lean manufacturing, are becoming common platforms in the biopharma sector worldwide. In contrast, Indian biopharma developing biosimilars still rely hard on older technologies and remain to adopt these new norms, allegedly citing justifications, such as the lack of relevance or the cost pressure. A holistic view of project planning and risk assessment in terms of resources and timeline is critical to manage cost pressure. The development and implementation of balanced a quality management system (QMS) will reduce the cost of production and protect the data through an achievable and retrievable system. It also controls equipment and process management. Use of QMS can greatly manage the time for process development and application for approval process. Although adopting 'single use' has gone up in Indian biopharma recently, stainless steel systems in manufacturing still dominate. Moreover, many are yet to deploy sophisticated analytical tools [102].

7.9. Lack of Internal (Industry-Exposed) Expertise

In terms of having the right knowledge ecosystem and pool of talent, India is critically lagging. The Indian education system is still very theoretical and hardly exposes graduates and post-graduates to a high level of practical hands-on experience, particularly in the biopharma sector [103–106]. Most universities and academic institutions in India are not research oriented and highly theoretical. The curriculum designed by the institute is based on theoretical approaches and only the related practical programmes. However, these curricula do not encourage including the factual issues and possible solutions through life science and practical problem-solving approaches. Many business leaders and senior managers in the Indian biotech sector emerged from the run-of-the-mill pharma base and struggle to fully understand and cope with the fine nuances of new-age biotech

drug development. This results in misaligned processes and analytics not meeting the regulatory expectations. Obviously, the regulators will be eagle-eyed on quality that would seemingly pose a challenge to Indian companies. There is hardly any curriculum covering quality culture or taught in any Indian university or higher education program, exposing young professionals to a global regulatory framework and quality culture. It has resulted in a few drugs being barred in key overseas markets in recent years, a distraction for Indian biopharma manufacturing hubs. The hard reality is that many Indian biotech drug makers are still struggling to fix such regulatory issues in quality manufacturing operations. The companies should design and timely assess need-based training programmes. Such training will create the opportunity to develop skill sets related to industry and job-specific techniques, e.g., leadership, management, general business, manufacturing, finance, and the overall techno-management. Biocon academy is a trendsetter in an industry-ready workforce, offering interdisciplinary courses, helping professionals and technicians grow through industry–academia interaction.

7.10. Budget-Funding

In developed markets, e.g., the US [107], UK [108], EU [109], etc., most of the biotech innovation is fueled by small-time emerging bio-ventures primarily funded by angel investors or venture capitalists. Through alliances, collaborations, or acquisitions, new technological platforms or discoveries eventually find their way to significant biotech companies. In India, however, the lack of new and small biotech companies with creative platforms is more pronounced. Investors won't put their faith in the little Indian biotech start-ups because of their perception of them as cheap global manufacturing hubs or as companies creating low-cost knockoffs of popular medicines. An overly ambitious company plan, a lack of a focused execution strategy, inadequate risk management, and a lack of planning ahead of time all contribute to start-up failure. Lack of significant, effective industry–academia relationships and a suitable entrepreneurial ecosystem to support biotech start-ups are detrimental and eventually lead to failure in capturing a suitable market with a particular client base [110–112].

7.11. Market Needs and Response to Competitive Pressures

With a thriving domestic biosimilars market, India ranks first in the number of approvals (98), but the country's guidelines for biologics development are not considered to be as effective as those by the US and the EU, or the WHO in general. To address the issues and challenges associated with developing biosimilars, the Central Drugs Standard Control Organization (CDSCO) in collaboration with the Department of Biotechnology (DBT) developed 'Guidelines on Similar Biologics: regulatory requirements for marketing authorization in India' in 2012 and revised it in 2016. It endeavors to align it with international agencies like EMA, USFDA and the WHO [113].

Notwithstanding the domestic regulatory framework, a few of the mandatory global aspects for the biosimilars regulatory requirements immediately applicable to India are:

1. Interchangeability: FDA needs 'an interchangeable biological product which is similar to an existing FDA-approved reference product'. This allows substitution of the reference product with the interchangeable biologic by a pharmacist without the interference of the clinician who prescribed the reference biologic [114].
2. Naming: WHO follows the International Non-proprietary Name (INN) for generic products. Several other countries have adopted their unique naming convention. EU follows INN while Japan adopt INN with BS as suffix, US also follows INN with four-letter suffixes [115].
3. Labelling: After approval, the insert should clearly indicate whether the data were generated on a similar biologic or innovator product, including differences in characterization and the extent of similarity with the reference biologic on safety, immunogenicity, and efficacy for the awareness of patient and professionals. Moreover, the COOL (country of origin labelling) law applies, since 2003 [116].

7.12. Filling the Gaps in International B2B and B2C Collaborations, and Handholding

Despite decades of dominance by the generic medicine sector, India's participation in the race to produce complex biotech medications, a worldwide market worth tens of billions of dollars, is quite pitiful. While there are few such items available on the local market in India, where regulatory barriers are relatively low, South Korean, American, and European companies are quickly catching up in the race to supply the lucrative Western markets. Only three Indian companies, Biocon, Dr. Reddy's Laboratories [117], and Intas Pharmaceuticals, have partnerships that are effective in developing biosimilars for the Western (US and EU) markets [118].

For many smaller Indian players, the expense and complexity of creating biosimilars have acted as major barriers. The three Indian start-ups that have announced aspirations to produce biosimilars for the US and Europe have all teamed up with more established Western enterprises. Through a partnership with Mylan Inc., four compounds are being tested by Biocon in Phase III trials. The testing criteria in India do not adhere to the USFDA, EMA, and WHO norms, which many nations with biosimilar markets either adopt or model through their own national guidelines. This is a major problem for India's attempts in international biosimilar trade. Indian biosimilars must pass the tests in accordance with what is generally regarded as scientifically sound for them to be taken seriously by international regulators. Ideally, a worldwide uniform approach to biosimilar approval would consider the current regional variations in rules and ensure that the 'head-to-head' similarity concept at the center of strong guidelines from the EMA, FDA, and WHO is retained [119,120].

Historically, many Indian biosimilars had to revisit their product development strategy to stand a chance in the US market. Many believe that India's technical expertise, vast experience with the generics' development, and the huge density of scientists will help them overcome international challenges. Indian biosimilars market remains robust, as evidenced by the large number of biosimilars, and there have been international successes in a few cases too. Biocon is one such example of an Indian biopharmaceutical company successfully entering the US market [121].

7.13. Lack of Diversification

The present Indian biotech industry has its roots in the traditional generic pharmaceutical industry. The $15 billion pharmaceutical sector in India has long been based on copying chemical medications. However, because biotech medications are more challenging to produce and duplicate, authorities have developed the idea of equivalent versions that are functionally equivalent. Though biotech medications that need genetic engineering make up an increasing portion of innovative medications, the outlook for copycat medicines is dismal and they will move into the straightforward small-molecule pharmaceutical category. As was previously said, Indian biopharma is hampered by a lack of trained and qualified personnel. The Indian pharmaceutical industry should make investments in training and human resource development to maintain the effectiveness of its talent pool. The personnel should receive ongoing training that covers technical topics as well as current regulatory rules, international standards, and patent laws, among other things. Late bloomers, such as China [122–124] and Korea, moved far more quickly by partnering with significant international firms of the highly regulated international market than India, who joined the biosimilars market first. Most manufacturing facilities adhere to cGMP and are regularly accredited by the FDA and EMA, giving them access to international collaboration. The regulatory investment opens the platform for multinational trials, and they are implementing policies similar to those used on a global scale to improve the quality and credibility of clinical trials. In contrast, the Indian biopharma sector is having problems due to a lack of policy support and pricing control. They are mostly moving toward biobetters (better safety and effectiveness profiles, enhanced ADME-Tox profiles, less side-effects, increased functionality, longer stability, better formulation, etc.) or cutting-edge biotech medications throughout time. Sadly, India still places a lot of emphasis on

the traditional biosimilars, particularly those that are losing their patents. This leads to unhealthy competition and little to no distinction. Before biosimilars were introduced to Europe in 2006, they were already available in India in the early 2000s. The first biosimilar was introduced on the market in the US following the recent introduction of a regulatory guideline [125–127].

India's experience has not been good. Intas, for instance, recently received reports of patients on its biosimilar version of Roche's eye drug Lucentis developing inflammation barely two months after the drug was launched [128]. The CDSCO and DBT guidelines have enabled manufacturers to bypass Phase III clinical trials in circumstances where sufficient pharmacodynamic (PD) and pharmacokinetic (PK) data are available, opening the floodgate for faster product approval. As such, drug developers in many emerging countries including India face heightened scrutiny related to data integrity breaches. Such a plan to bypass phase III for biosimilars could be a serious global concern in times to come. It can raise questions on the GMP of related manufacturing companies, difficulty in penetrating global markets, and create concern among patients and physicians on the quality and safety of the biosimilar.

Having a system in place that defines what tests need to be done is critically important. Guidelines have relieved Indian manufacturers of conducting redundant studies, making the process of bringing a product to market more feasible. Prior to the revisions, a reference product needs approval and marketed in India if the manufacturer desired its biosimilar to treat as that of a reference product. The alterations allow Indian companies to develop biosimilars based on reference products approved by the US, European Union, Japan, Canada, and Switzerland [129]. Additionally, CDSCO and DBT included a requirement for Phase IV trial post marketing, which must include at least 200 trial volunteers and be conducted within two years of market approval [130].

Most Indian companies engaged in biosimilars manufacturing do not attempt to crack the US market. There seems to be eagerness from Europe and South America to develop and expand biosimilars in the US. The manufacturing process of quality biosimilars is complex. The regulatory frameworks in US are stringent, having broad IP and patent laws, which may lead to a major obstacle in effective marketing leading to patient inaccessibility and cost-increase. Different pharmaceutical companies are already in the global market, providing tough competition. The cost of litigation, if any, is quite a high burden on Indian companies which forces them to shy away. Biocon has been willing to battle out with patent-holders in court. In March 2020, for instance, the company won a court-ruling that invalidated a Sanofi patent which attempted to block Biocon and Mylan from commercializing an insulin product, Glargine, in the US [131,132].

7.14. Regulatory Affairs and IPR

Indian regulations stem from biosimilar guidelines originally drafted in 2012 (revised in 2016) by two Indian agencies, the Central Drugs Standard Control Organisation (CDSCO) and the Department of Biotechnology (DBT). There are conflicting opinions on whether the revision of the guidelines has made a difference in ensuring the 'inspired' biosimilars perform similar or better than their originator (inspirer/reference) products.

The patent expiry of many largely successful biologicals has paved the way to develop biosimilars as alternative to the otherwise high-cost biological therapies [133,134]. Given the complexity of biologicals, the regulatory guidelines for biosimilars approval are meticulous and different from the generics. Hence, biosimilar developers often face issues in applying for evaluation by regulatory authorities. With large number of biosimilars at the development stage, a deeper understanding of the regulatory approval process by the manufacturer is needed. A major deficiency identified is the comparability between the proposed biosimilar and its reference biological. As stated earlier, there are conflicting opinions on differentiating between the 'inspired' biosimilar and the 'inspirer' product. Regulatory bodies recommend a three-tier comparability approach to gain regulatory approval for biosimilars, viz., analytical characterization, preclinical trials, and clinical studies. Many

applications from India stall due to a failed pharmacokinetic (PK) comparability study. PK studies are considered more sensitive to detect product-related differences. Process validation is another major issue, wherein the common deficiencies observed relate to the process controls, validation of equipment sterilization, vials-filling strategy, profiling impurities, and the stability of the bioactive substance/product.

It is important for biosimilar manufacturers to understand the reference molecule via an in-depth analysis and identify critical quality attributes (CQAs) that may impact the safety and efficacy of the biosimilar. The manufacturer needs to design a process and establish appropriate process controls to ensure product reproducibility and process repeatability with consistent product quality. Stability studies are critical to demonstrate the shelf-life and sustained quality of products. To develop biosimilars, the manufacturer must follow good manufacturing practises (cGMP) and good clinical practises (GCP) for adequate cGMP and GCP compliance as may be desired by the regulators [135–137].

Regulatory experience of biosimilar manufacturers reveal that most rejections were due to the gaps in the manufacturer's understanding of regulatory expectations from a comparability exercise, and cGMP and GCP compliance. Manufacturers must learn from experience with time, leading to fewer rejections. Although Indian guidelines are revised, they still fall short on various counts, including animal testing. For instance, the guidelines suggest that monoclonal antibodies (mAbs) be tested on rats, which will obviously provide limited valuable data on the efficacy of the drug on humans. Immunogenicity tests to measure the potency of a biological agent to stimulate an immune system response are conducted solely in animals, which fails to provide a full picture of how biosimilars will influence humans, owing to dissimilar metabolic responses [138–140]. mAbs have no toxicity in rodents as they do not possess the complimenting receptors. The efficacy and safety testing can be performed in 3D cell culture and xenograft model which often exhibit more similarity to in vivo tissue organs regarding gene/protein expression profiles [141]. The CDSCO in 2016 had established guidelines based on WHO specification. mAb characterizations are also consistent with the WHO framework. It defines in vitro cell-based assays for cell proliferation, cytotoxicity, receptor binding, and neutralizing assay but safety and in vivo PK/PD criteria are still ill-defined. The biological assays are determined, but the types of assays are not specified. Biosimilars must be similar to the reference products in terms of safety and efficacy, so the needed tests and their results are critical. Drugs should not significantly exceed the efficacy of the reference product they are intended to imitate, as a biosimilar with greater potency than the reference product may have more serious latent adverse effects. Improper standards may mean some products do not truly qualify as biosimilars; the drug being effective does not prove to be biosimilar. Moreover, as many Indian trials recruit fewer (100 or so) volunteer participants, the statistical validity of such trials is questionable.

Unlike in the US, India does not require biosimilars to pass an 'interchangeability' test, allowing the pharmacists to switch patients from reference products without physician permission. The US is the only nation requiring a biosimilar interchangeability designation. This designation limits patients' access to cheaper biologics. Another big difference is the perception of biosimilars. Whereas the US physicians and patients may be uninformed or misinformed about the safety and efficacy of biosimilars, the Indian government encourages people to search for and adopt cheaper alternatives. Statistics suggest that the Indian population is more price-sensitive on healthcare. Many households do not have health coverage, and 82% of healthcare costs in India are paid out of pocket. A cheaper alternative for a prescribed drug, therefore, will naturally hit the market. Another difference in views between India and the US is the rate of uptake of biosimilars. This rate is rapidly growing in India, and a bigger reason for this is the high cost to private investors in pharmaceuticals research and development, making the advanced drug too costly for the commoners' reach [142–145].

8. Indian Vaccines in the Global Market

India has experienced a momentous journey from being an importer to the largest global exporter of vaccines of immediate and long-term healthcare significance. India contributes nearly 50% of the global vaccine demand for immunization programmes. King Institute, Guindy in Tamilnadu was established as a BCG lab immediately after Indian independence, in 1948. Subsequently, India led in the production and export of six vaccines (BCG, TT, DPT, DT, polio, and typhoid) for children under the expanded immunization programme, and Measles vaccine was added to the list later in 1985 [146]. Similar to the global scenario until the 1980s, vaccine requirements in India too were primarily fulfilled through government institutions. This could be attributed to the fact that the Indian public sector lacked an access to novel technologies to produce vaccines for TT, DT or DTP, or the scale-up production of oral polio or the measles vaccines. In 1987, the Bharat Immunologicals and Biologicals Corporation Ltd. (Bulandshar, India) was established by the Department of Biotechnology, Government of India in technological collaboration with the Institute of Poliomyelitis and Viral Encephalitis (Moscow, Russia). The production was initially restricted to the repackaging of OPV that was imported in bulk from the Russia [147]. The second phase targeted at indigenous OPV production in the next five years. The Indian Vaccine Corporation Ltd. (IVCOL), Gurgaon, Haryana initiated indigenous measles vaccine production in technological collaboration with Institut Merieux, Lyons, France. However, it could not peak further as the private sector that acquired the Institut Merieux denied transfer of technology to IVCOL. IVCOL was shut down, and India imported measles vaccine to fulfil its requirement until the Serum Institute of India (SII), Pune started its supply to the Expanded Programme on Immunisation (EPI) EPI (now called Universal Immunisation Programme (UIP) in India) in 1992 [147].

The Hepatitis B vaccine launched in 1990 became the game changer [148]. The Indian private sector took the driver's seat gradually and launched several vaccines, e.g., influenza, MMR, and chickenpox, that found their way into regular global immunization projects. Since then, driven by the increased investments and favorable government policies, the Indian private sector vaccine market revenue reached US $95 billion in 2020. As it stands now, the Serum Institute of India Pune, Indian Immunological Limited (a subsidiary of National Dairy Development Board), BCG Chennai, BIBCOL Uttar Pradesh, Wockordt Limited Mumbai, Shanta Biotech (Sanofi) Hyderabad, Zydus Cadilla Pharma Ahmadabad, Bharat Biotech, Biological E, Panacea Biotech, etc. represent the major vaccine producers [147]. Indian vaccine industries, especially Serum Institute and Bharat Biotech Ltd., played a significant role in the global vaccination drive during the COVID-19 pandemic (Tables 2 and 5) [149]. Amid the rising Monkeypox (MPX) cases in India, the Serum Institute of India (SII) is set to manufacture a vaccine against it [150]. The National Institute of Virology (NIV, Pune) could successfully isolate MPX virus from a patient sample to help develop vaccine and test kits (https://www.livemint.com/news/india/monkeypox-8-cases-in-india-so-far-1-death-10-things-to-know-11659430193160.html, 8 October 2022). Vaccine manufacturers and vendors need to collaborate with the healthcare systems and researchers to earmark the global need for the production scale-up. Collective regional and global partnerships are highly imminent to strengthen and execute the action plans.

9. Visionary Perspective and Conclusion

Around 20% of generic medications and 62% of vaccines are now supplied by the Indian pharmaceutical industry, which has emerged as the world's leading supplier of pharmaceuticals (by volume). A very positive sign was the remarkable work done during the most recent COVID-19 pandemic. India's biopharmaceutical industry has been instrumental in producing and supplying treatments to fight COVID-19 since the first days of 2020. Industries increased their output to provide more than 133 nations with high-quality, reasonably priced medications despite a weak supply chain and a lack of labor. Six Indian pharmaceutical companies are currently producing the antiviral medicine "Remdesivir" due to strong demand and distribution in 127 countries to combat the continuing pandemic.

In India, 30 groups from the pharmaceutical industry and academia are working on the COVID-19 vaccine, and most of them have received preliminary approval for use in an emergency. India is making good progress with its immunization campaign. As previously described, there are gaps in effective translational research on Indian soil that must be promptly and appropriately filled. The adoption of cGMP in various manufacturing firms with accreditation from international regulatory bodies and the improvement of regulatory rules on a worldwide scale will encourage Indian producers of biosimilars to compete on the global market [151]. Innovations, working with other sectors of the economy, and promoting training programmes to keep a strong scientific workforce will help to advance to world-class potential. The government has several programmes for the start-ups for small and medium biotech enterprises, industry-academia collaborations, and translational research. Such inventiveness would help the Indian biopharma sector to improve its global competitiveness and reach the target of a US $5 trillion economy by 2025. The two major areas for governmental support and interventions are the state-of-art technological infrastructure and the high-end industry-ready trained manpower. These two should follow a proactive and encouraging handholding in terms of administrative and regulatory frameworks in the spirit of 'ease of doing business'. The time is ripe to grow our economy through evolution in the biotechnology and biopharma sector. Innovation demands a strong and effective collaboration among university, industries, and incubators. Public-private partnership should nurture more start-ups and take steps for skill development, where we are lagging. India needs to learn the investment strategy, development of innovative and managerial skills, adoption of new techniques, collaborations, and business models from countries, such as Israel, South Korea, Japan [152,153], China [154], and USA. Indian society and the mindset of its people should be supportive towards a risk-taking attitude and encouraging to innovation driven changes. By empowering technopreneurs to develop from small and medium enterprises to large industrial scale operations, India will be able to take innovative thoughts to the global level and ultimately realize an '*Atmanirbhar Bharat*' (self-reliant India).

With a detailed and closely researched compilation of the state-of-art facts and figures, this article is an effort to provide a 360° view of how Indian biosimilars and vaccines could replicate the success of pharmagenerics at the global stage. However, as is universally accepted for scientific works, there are few limitations as well. They are pointed out below. Firstly, the details about the performance of the upcoming and greenhorn (start-up) companies in this greenfield sector are lacking and rather unorganized wherever they are available. Secondly, there are few such new-age biosimilar products which are quite difficult to differentiate from the biologics, thus making the picture on the financial projections and global demand trends for biosimilars alone hazy. Thirdly, being a greenfield sector, the sectoral dynamics remains ill-understood. Fourthly, the majority of the potential biosimilars and vaccines products are at various stages of their development in India and elsewhere, and their ultimate impact on the overall global biosimilars scenario will be clear in due course of time. Finally, India replicating its success in pharmagenerics in the innovation and research-intensive field of biosimilars and vaccines at the global stage would have to face strong challenges from countries, such as the US, China, Korea, Japan, and the European Union, which will be revealed better with the passage of time.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/vaccines11010110/s1, Supplementary Materials S1: Indian biopharma R&D major industries and their products; Supplementary Materials S2: Government and private initiatives. Refs. [155–175] are cited in Supplemental Materials.

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Review

Systematic review of arts and culture-based interventions for people living with dementia and their caregivers☆

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ABSTRACT

Aims: To explore and summarize studies investigating the effect of arts and culture interventions for people living with dementia and their caregivers on the well-being and cognition of the person living with dementia and, caregiver strain.

Methods: We carried out a systematic search of five electronic databases (PubMed, PsychINFO, Embase, CINAHL, and Cochrane Library). We included original research published in peer-reviewed journals including both qualitative and quantitative studies. We assessed quality of included studies using the Cochrane Collaboration's Risk of Bias tools. A narrative synthesis was conducted of all included studies.

Results: Of the 4827 articles screened, 34 articles met inclusion criteria. A variety of interventions were identified, with more than half taking place in a museum or gallery. Five RCTs showed improvements in wellbeing outcomes but no cognitive improvements except in some subscales in a music intervention. Most non-randomised studies reported cognitive improvements and well-being improvements for people living with dementia and their caregivers. Studies primarily focused on individuals with mild to moderate dementia.

Conclusions: The use of arts and culture interventions may provide benefits for people living with dementia and their caregivers. However, heterogeneity of the interventions and outcome measures prevented generalization of the results. Further research of arts and culture interventions for people living with dementia and their caregivers should utilize larger controlled trials, standardized outcome measures and include individuals with moderate to severe dementia.

1. Introduction

Dementia is a neurocognitive disorder in which there is a cognitive decline in one or more of the domains of attention, executive ability, learning and memory, language, perception, praxis and social cognition (American Psychiatric Association, 2013). Based on current trends, the number of individuals living with dementia will increase dramatically from 57 million people currently living with dementia worldwide, to 152 million by 2050 (GBD, 2019). Approximately 40 % of people living with dementia (PLWD) suffer from reduced well-being and depression (Alzheimer's Association, 2019; Leung et al., 2021) Well-being comprises of physical, social and mental domains which can be split into 'hedonic' well-being is centred on feelings such as 'happiness' or 'anxiety' and, 'eudaimonic' well-being which centres on the 'thinking' aspects such as 'life satisfaction' or 'quality of life' (CDC, 2018; Clarke et al., 2020; Dolan and Testoni, 2016). Caregivers of individuals living with dementia often experience negative mood changes due to the challenges of caring for someone with dementia, sometimes referred to as caregiver strain (Brodaty and Donkin, 2009). Caregiver strain can present with symptoms including exhaustion, social withdrawal, sleeplessness, irritability, depression, and anxiety (NHS, 2018). As one of the seven targets of the World Health Assembly's action plan, cultivating positive well-being for people living with dementia and dementia caregivers has become a priority for many health, social care and community organisations.

Over the last few decades extensive research has shown the positive

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effects of creative arts therapies on the mental health and well-being of the general public and of varying patient populations (Regev and Cohen-Yatziv, 2018; Reynolds et al., 2000; Slayton et al., 2010). There have been documented benefits of art therapies in the prevention of cognitive decline in adults living with mild cognitive impartment and on the well-being of people living with dementia (Emblad and Mukaetova-Ladinska, 2021; Lee et al., 2019). Creative arts therapies come in many different forms from visual art therapy, music therapy, to dance therapy. However, creative arts therapies can be differentiated from arts and culture-based interventions. A key aspect of art therapy interventions is that they are delivered and designed by trained art therapists rather arts and culture interventions are arts activities that are delivered by researchers, trained facilitators, educators or volunteers (Rubin, 2009). Creative art therapies can be defined as, ‘ a form of psychotherapy that uses art media as its primary mode of expression and communication’ (BAAT, 2022). Whereas arts and culture interventions can be defined as any creative activity involving, “collections, combined arts, dance, libraries, literature, museums, music, theatre, and visual arts” to encompass all forms of creativity (Arts Council England, 2021).

Research has shown the arts and creative actives play an essential role in individual health in the general population (Fancourt and Finn, 2019, 2020). Participation in arts and culture activities have been demonstrated to provide personal, physical and psychological benefits resulting in emotional and cognitive changes such as reduced stress, depression and reduced symptoms and feelings of burden of chronic conditions (Camic, 2008; Lee et al., 2021; Stuckey and Nobel, 2010). In-line with growing calls for non-pharmacological interventions for people with dementia and research on the benefits of the arts on ageing, there has been increasing interest in the role arts and culture interventions can play in dementia care (Camic et al., 2018; Cohen, 2009).

Several systematic reviews have been undertaken to investigate the effectiveness of arts activities for people living with dementia (Cavalcanti Barroso et al., 2020) but have only looked at specific forms of interventions such as art-making activities. A recent review was the first of its kind to examine the benefits of multiple different types of cultural activities on people living with cognitive impairment, which found significant improvements in general cognition quality of life, emotional wellbeing and reduction in depressive symptoms (Delfa-Lobato et al., 2021). Carers were often excluded from arts and dementia research or are studied separately from the individual they care for, indicating a clear gap in the literature. To our knowledge, there have been no reviews to date that explore a range of arts and culture interventions and their impacts on both individuals living with dementia and their carers. This review aimed to fill the gaps in previous reviews by providing context to the scope of existing arts and culture interventions while examining these interventions for their effects on the cognition of people living with dementia and the well-being of both individuals living with dementia and their carers.

2. Methods

We used Arts Council England’s definition of culture to define the various types of arts and culture interventions to be included.

2.1. Protocol and registration

The review protocol was registered on PROSPERO, an international prospective register of systematic reviews (Registration ID: CRD42021236325). Methods for this systematic review followed guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

2.2. Search Strategy

We conducted electronic database searches of PubMed, PsychINFO, Embase, CINAHL and the Cochrane Library from inception to February 15th of 2021. Search terms covered six areas listed below and were combined using the AND Boolean operator. We set no limits in terms of language or publication date. Search terms were modified to match terms in each database.

- Dementia: Alzheimer’s OR AD OR ADRD OR VaD OR dement*
- Caregiver: caretaker OR informal caregiver OR carer
- Intervention: interventions OR strategies OR best practices OR program* OR trial OR study OR education OR training
- Outcomes: Well-being OR wellbeing, OR well being OR QOL OR Quality of Life, caregiver stress OR caregiver fatigue OR caregiver burnout OR caregiver strain OR caregiver burden
- Cultural Institution: Museum OR Heritage site OR library OR archive OR gallery or Theat*

2.3. Eligibility criteria

- Study Design: Original research published in peer-reviewed journals describing qualitative and quantitative studies (randomised controlled trials and non-randomised pre/post designs, cohort studies, mixed-method descriptive studies, longitudinal studies, or observational studies) were included. Conference abstracts, letters, reviews and non-peer-reviewed articles were excluded.
- Population: individuals living with dementia and informal caregivers. Informal caregivers were defined as non-professionals who care for the person living with dementia full or part-time. No limits regarding age, gender, race or educational background were set. Studies of participants without a dementia diagnosis or included only specific forms of dementia-related neurogenerative conditions such as Parkinson’s, Huntington’s, Multiple Sclerosis, etc., were excluded. Studies that included only professional caregivers were excluded. Studies that did not include relevant outcomes for the person with dementia and/or their caregiver were excluded.
- Intervention: All cultural or arts-based interventions, strategies, activities and programming studies for people living with dementia or carers to people with any form of dementia as defined by Arts Council England’s definition of culture. Non-arts or culture-based interventions were excluded. Interventions with a therapy-based approach were excluded. Interventions based on ‘healthy lifestyles’ such as diet or exercise routines were excluded. Pharmacological interventions were excluded.
- Comparison: Studies with or without comparison groups, comparisons within the same group pre- and post-intervention or with a group not receiving an intervention were included.
- Outcomes: Studies using qualitative methods or quantitative measures such as the mini-mental state examination (MMSE) or QoL-AD to evaluate participant outcomes of cognitive capabilities and psychological health and well-being were included. Studies that did not provide an outcome analysis or without clear outcome measures were excluded. Studies reporting outcomes unrelated to the well-being of people living or carer, or outcomes unrelated to the cognition of people living with dementia

2.4. Study Selection and data extraction

We conducted searches in each online database separately and exported all retrieved articles to Covidence systematic review software (Covidence, 2020). After removing duplicates from the search results, two authors (PL and SA) independently screened all titles and abstracts against pre-specified selection criteria. PL and SA then independently assessed the full text to determine if selection criteria were met. Specific reasons for exclusion were recorded and disagreements between authors were resolved. Reference lists of included papers and related systematic reviews were screened for potentially relevant articles.

One author (PL) extracted data using Covidence systematic review software, and outcome domains were cross-checked by a second

reviewer (SA) to ensure completeness of extraction. Extracted data included study and participant characteristics, intervention methods, and outcome measures. A narrative synthesis approach was utilised to summarise the results and accommodate the complexity of the various types of interventions and to provide clear outcome themes.

2.5. Quality assessment

Due to broad inclusion criteria, we used two risk of bias tools to assess study quality. To assess randomised controlled trials (RCTs), we used the Cochrane Collaboration's Risk of Bias Tool (The Cochrane Collaboration, 2021), which gauges the risk of bias for sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. For non-randomised, mixed-method, and quasi-experimental studies, we used the Cochrane Risk of Bias in non-randomised studies tool (The Cochrane Collaboration, 2021), which gauges the risk of bias due to confounding, selection of participants into the study, classification of interventions, incomplete outcome data, selective outcome reporting, and other sources of bias. Each study was evaluated for each criterion as low, unclear, or high risk of bias. These appraisal tools were selected as they are well-established tools with clear guidance for reviewers, ensuring transparency and minimising bias. After rating each paper independently, the reviewers (PL and SA) met to discuss and resolve any disagreements.

3. Results

3.1. Study selection

Our search resulted in 4827 studies with 2068 duplicates. 2759 studies remained for title and abstract screening. 233 full-text articles were assessed, and thirty-four articles fit the inclusion criteria. The PRISMA flowchart is shown in Fig. 1.

3.2. Study characteristics

A total of 34 studies were included, from the United Kingdom as well as thirteen other countries. Eleven were qualitative studies, 13 used only quantitative assessments and 10 used mixed methods assessments. Five studies were randomised controlled trials. Most studies assessed well-being and cognition for participants living with dementia and assessed the quality of the relationship between the caregiver and the person they care for.

All studies included people living with dementia and informal caregivers of people living with dementia. Eight studies reported the mean age of individuals living with dementia; which was 74.8–84.4 years old, three studies reported the mean age of caregivers which was 62.9–71.1. Twenty of the included studies disclosed the gender ratios for people living with dementia; seven studies reported the gender ratios for caregivers. Most of these studies had more female than male participants with 63 % female participants living with dementia and 75 % female carers. Ten studies did not provide caregiver demographics alongside caregiver data, and 9 studies only provided the number of participants living with dementia and caregivers without gender ratios or mean ages. Five studies did not specify dementia severity. The majority of studies concentrated on individuals living with mild to moderate dementia with only one study centring on people living with moderate to severe dementia. Only seven studies took place in long-term care facilities, with the majority of studies conducted in community settings such as museums, community art centres or day care facilities. The majority of interventions were provided for about six weeks with the longest

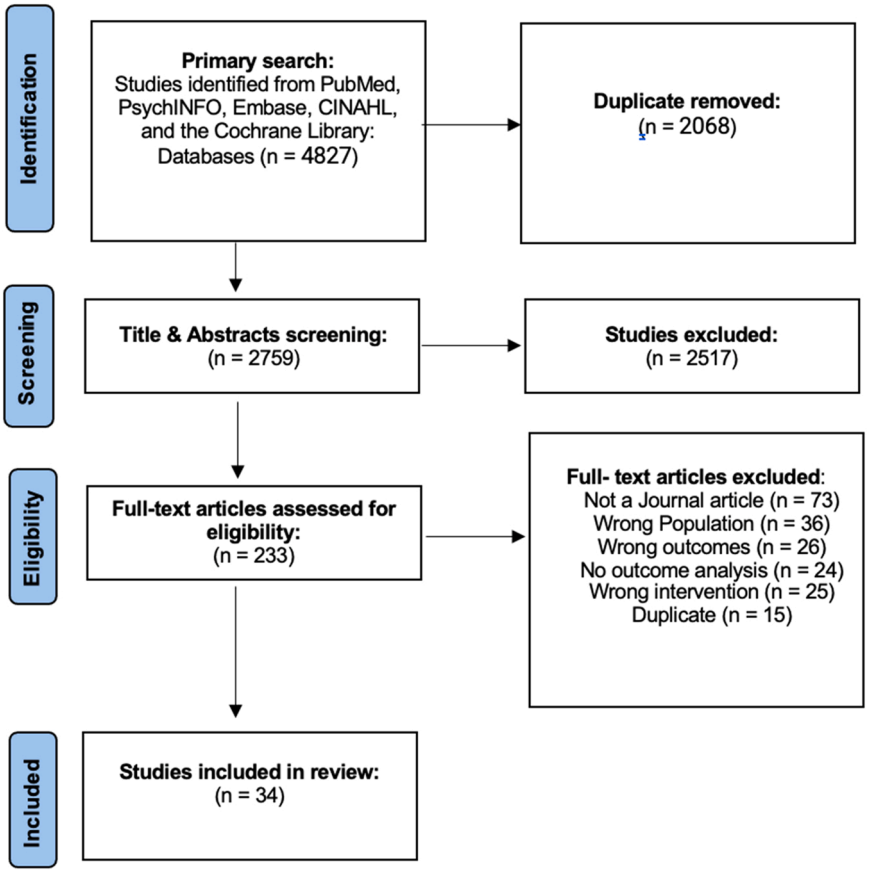

Fig. 1. PRISMA flow diagram.

intervention running seven months and the shortest a one-time session. Four studies did not specify how long the interventions were conducted. Characteristics of included studies are presented in Table S1. Breakdowns of quality assessment and risk of bias can be found in Appendix A.

3.3. Narrative synthesis of intervention effects

All thirty-four studies were classified into five main intervention types: Museum and Gallery interventions with an art-making activity (n = 9), Museum and gallery interventions with other activity (n = 8), Art-making interventions (n = 6), Music-based interventions (n = 4), and Other Interventions (n = 7) that did not fit into the previous four categories. Of the thirty-four included studies, thirty-two measured for changes in well-being. Of the thirty-four included studies, twenty-five measured for changes in cognition.

3.4. Museum and gallery interventions with an Art-Making activity

Nine studies assessed the impact of Museum and Gallery interventions with an art-making activity. These interventions were delivered by museum or gallery educators or by community artists. In two studies these facilitators received dementia awareness training prior to the intervention (Windle et al., 2018; Young et al., 2015), one study was led by a community artist with previous experience working with people living with dementia (Windle et al., 2020). Five of these studies focused on individuals living with mild to moderate dementia (Camic et al., 2014; Eekelaar et al., 2012; Flatt et al., 2015; Schall et al., 2017; Young et al., 2015), three studies included all dementia severity levels (Belver et al., 2018; Newman et al., 2019; Windle et al., 2018) and one study did not specify dementia severity (Windle et al., 2020). Participants were recruited from aging and dementia services, community venues, and care homes. The number of people living with dementia-carer dyads ranged from six to one hundred. Eight of the nine studies used weekly sessions ranging in duration from 3 weeks to 3 months, and the other delivered a single-session intervention (Flatt et al., 2015). A variety of study designs were employed to evaluate the interventions such as pre- post mixed-methods (Camic et al., 2014; Eekelaar et al., 2012; Newman et al., 2019; Windle et al., 2020, 2018), qualitative (Belver et al., 2018; Flatt et al., 2015), exploratory (Young et al., 2015) and RCT (Schall et al., 2017). Six studies used both qualitative and quantitative measurements such as interviews, Quality of Life questionnaire for people with dementia (DEMQOL)(Smith et al., 2005) and mini-mental status examination (MMSE)(Folstein et al., 1975) (Camic et al., 2014; Eekelaar et al., 2012; Newman et al., 2019; Schall et al., 2017; Windle et al., 2018, 2020). Three studies employed solely qualitative measures such as interviews and session recordings (Belver et al., 2018; Flatt et al., 2015; Young et al., 2015).

3.5. Cognitive outcomes

Eight of the nine studies measured cognition in people living with dementia (Belver et al., 2018; Camic et al., 2014; Eekelaar et al., 2012; Flatt et al., 2015; Newman et al., 2019; Schall et al., 2017; Windle et al., 2018; Young et al., 2015). Five studies demonstrated that the intervention was associated with positive changes in cognition, including improvements in memory, verbal fluency and communication for people living with dementia (Belver et al., 2018; Eekelaar et al., 2012; Flatt et al., 2015; Newman et al., 2019; Young et al., 2015). The remaining three studies reported no improvements to cognition although in one qualitative interview study, caregivers observed the person living with dementia as more present and engaged during the intervention than normal (Camic et al., 2014). Four studies reported improvements in memory, however, these studies used un-coded qualitative measures (Eekelaar et al., 2012; Flatt et al., 2015; Newman et al., 2019; Young et al., 2015). Three studies reported improvements in communication between the person living with dementia and their carer (Belver et al., 2018; Newman et al., 2019; Young et al., 2015) and one study reported a worsening in communication (Windle et al., 2018).

3.6. Well-being outcomes

Eight studies measured well-being and quality of life (QoL) (Belver et al., 2018; Camic et al., 2014; Eekelaar et al., 2012; Flatt et al., 2015; Newman et al., 2019; Schall et al., 2017; Windle et al., 2018, 2020). Five studies reported improvements to the overall mood in individuals living with dementia (Belver et al., 2018; Flatt et al., 2015; Newman et al., 2019; Schall et al., 2017; Windle et al., 2018). Three studies reported improvements to self-esteem for people living with dementia (Newman et al., 2019; Windle et al., 2020, 2018). Three studies reported improvements in the relationship between the caregiver and PLWD through qualitative interviews with carers (Eekelaar et al., 2012; Newman et al., 2019; Windle et al., 2020). One study reported no significant changes to well-being for people living with dementia or caregivers, rather well-being remained stable over time (Camic et al., 2014).

3.7. Museum and gallery based interventions with non-art-making activities

Eight studies evaluated the impact of other styles of Museum and Gallery based interventions with a non-art-making activity. Four studies involved a museum or gallery visit accompanied by a discussion of the art and artefacts viewed (Colucci et al., 2010; D'Cunha et al., 2019; MacPherson et al., 2009; McGuigan et al., 2015). Two of these studies included an object handling session as part of the museum or gallery visit (Camic et al., 2019; Johnson et al., 2017). The remaining two studies included immersive reminiscence therapy as part of the museum visit and a story telling activity and art museum visit respectively (Kirk et al., 2018; Loizeau et al., 2015). These interventions were primarily delivered by museum or gallery educators. One study was delivered by specialist volunteers from the host museum (McGuigan et al., 2015). In two studies these facilitators received dementia awareness training prior to the intervention (Camic et al., 2019; MacPherson et al., 2009). Two studies did not specify dementia severity of participants (D'Cunha et al., 2019; McGuigan et al., 2015) and only one study, focused on individuals with any dementia severity (MacPherson et al., 2009). Participants were primarily recruited via local Alzheimer's associations, but were also recruited via local Alzheimer's societies, dementia services and hospitals. The number of person living with dementia-carer dyads ranged from 4 to 80. Six of the eight studies evaluated weekly interventions ranging in length from 6 weeks to 7 months (Camic et al., 2019; D'Cunha et al., 2019; Kirk et al., 2018; Loizeau et al., 2015; MacPherson et al., 2009; McGuigan et al., 2015). Two of the eight studies did not specify the frequency of intervention sessions (Colucci et al., 2010; Johnson et al., 2017). Three studies evaluated the intervention using a quasi-experimental pre-post design (Camic et al., 2019; D'Cunha et al., 2019; Johnson et al., 2017) two employed a qualitative design (Colucci et al., 2010; McGuigan et al., 2015), one a mixed-methods pre-post design (Loizeau et al., 2015), one was a randomized controlled trial (Kirk et al., 2018) and one study used a mixed-subject design (MacPherson et al., 2009). Seven studies used mixed measures such as qualitative interviews, Visual Analogue Scales (VAS)(Wewers and Lowe, 1990) and the Addenbrooke's Cognitive Examination (ACE)(Moisander and Huovinen, 2018) (Camic et al., 2019; D'Cunha et al., 2019; Johnson et al., 2017; Kirk et al., 2018; Loizeau et al., 2015; MacPherson et al., 2009; McGuigan et al., 2015). One study created a bespoke questionnaire to measure cognitive and well-being outcomes (Colucci et al., 2010).

3.8. Cognitive outcomes

Six of the eight studies used cognitive measures for people living with dementia (Colucci et al., 2010; D'Cunha et al., 2019; Kirk et al.,

2018; Loizeau et al., 2015; MacPherson et al., 2009; McGuigan et al., 2015). Five studies reported that the intervention was associated with improvements to cognition in individuals living with dementia (Colucci et al., 2010; D'Cunha et al., 2019; Loizeau et al., 2015; MacPherson et al., 2009; McGuigan et al., 2015) and one study reported no significant improvements to cognition (Kirk et al., 2018). Four of these studies reported improvements in memory using varied measurements (Colucci et al., 2010; D'Cunha et al., 2019; Loizeau et al., 2015; McGuigan et al., 2015). Three reported improvements in attention and engagement for people living with dementia (Loizeau et al., 2015; MacPherson et al., 2009; McGuigan et al., 2015). Four studies also reported improvements in communication and verbal fluency for people living with dementia (Colucci et al., 2010; D'Cunha et al., 2019; Loizeau et al., 2015; MacPherson et al., 2009).

3.9. Well-being outcomes

Seven of the eight studies measured well-being and QoL in people living with dementia and caregivers (Camic et al., 2019; Colucci et al., 2010; D'Cunha et al., 2019; Johnson et al., 2017; Loizeau et al., 2015; MacPherson et al., 2009; McGuigan et al., 2015). Four studies reported improved mood and overall well-being in both people living with dementia and their carers (Camic et al., 2019; D'Cunha et al., 2019; Johnson et al., 2017; Loizeau et al., 2015; McGuigan et al., 2015), one study reported these improvements only for people living with dementia (Camic et al., 2019). Three studies reported improvements to caregiver strain and the relationship between the carer and the people living with dementia (Colucci et al., 2010; Loizeau et al., 2015; McGuigan et al., 2015).

3.10. Art-Making interventions

Six studies assessed the impact of art-making activities on people living with dementia and their carers. The majority of studies were delivered by an artist. In one study the artist facilitators received dementia awareness training prior to the intervention (Shoesmith et al., 2020) one artist had previous experience working with people living with dementia (Perez-Saez et al., 2020). One study was delivered by trained student volunteers (Sauer et al., 2016). Two studies focused on individuals with any dementia severity (Kinney and Rentz, 2005; Perez-Saez et al., 2020), two on individuals with mild to moderate dementia (Richards et al., 2019; Shoesmith et al., 2020), one study included only individuals with moderate to severe dementia (Sauer et al., 2016), and one did not specify dementia severity (Pienaar and Reynolds, 2015). Participants were recruited from care facilities or through local Alzheimer's centres. The number of people living with dementia-carer dyads ranged from four to thirty-eight. Two of the six studies took place in a dementia day-care facility (Kinney and Rentz, 2005; Shoesmith et al., 2020), two studies were conducted in a long-term care facility for people living with dementia (Perez-Saez et al., 2020; Sauer et al., 2016), one study was conducted in the arts department of a university (Richards et al., 2019), and one study was held at a healthy aging café (Pienaar and Reynolds, 2015). Five studies used weekly intervention sessions ranging from five weeks to three months in duration. One study did not specify the frequency of the intervention (Kinney and Rentz, 2005). There were two pre-post studies (Perez-Saez et al., 2020; Shoesmith et al., 2020) and one used an ethnographic observational study design (Kinney and Rentz, 2005). One employed a qualitative evaluation design (Pienaar and Reynolds, 2015) and one study used an exploratory study design (Sauer et al., 2016). Only one study was a randomised controlled trial (Richards et al., 2019). Five of the six studies employed mixed methods such as qualitative interviews, Rosenburg Self-esteem Scale (ROS)(Rosenberg, 1965), GCWBT(Kinney and Rentz, 2005), MMSE, and QoL-AD(Logsdon et al., 2002) (Kinney and Rentz, 2005; Perez-Saez et al., 2020; Richards et al., 2019; Sauer et al., 2016; Shoesmith et al., 2020). One study used qualitative semi-structured interviews to explore participant experiences of the intervention (Pienaar and Reynolds, 2015).

3.11. Cognitive outcomes

Only one study measured changes in cognition, reporting that people living with dementia became more social, focused and mentally stimulated through the activities (Shoesmith et al., 2020).

3.12. Well-being outcomes

All six studies measured well-being and QoL for people living with dementia and carers (Kinney and Rentz, 2005; Perez-Saez et al., 2020; Pienaar and Reynolds, 2015; Richards et al., 2019; Sauer et al., 2016; Shoesmith et al., 2020). Two studies reported improvements to mood and overall wellbeing for people living with dementia (Perez-Saez et al., 2020; Sauer et al., 2016) Three studies reported improvements to mood and overall well-being for both people living with dementia and carers (Pienaar and Reynolds, 2015; Richards et al., 2019; Shoesmith et al., 2020). Four reported improvements to self-esteem for people living with dementia (Kinney and Rentz, 2005; Perez-Saez et al., 2020; Richards et al., 2019; Shoesmith et al., 2020). Three studies reported reduced caregiver strain and improvement in the relationship between the people living with dementia and their carer (Pienaar and Reynolds, 2015; Richards et al., 2019; Shoesmith et al., 2020).

3.13. Music-based interventions

Four studies evaluated the impact of music-based interventions for people living with dementia and their carers. Three studies evaluated singing (Bourne et al., 2019; Lee et al., 2020; Mittelman and Papayannopoulou, 2018), and the other evaluated music with movement (Cheung et al., 2014). Three of the studies were delivered by experienced musicians (Bourne et al., 2019; Cheung et al., 2014; Mittelman and Papayannopoulou, 2018). One study was delivered by a music therapist, however it was not considered a therapy-based intervention as it was not designed by a music therapist and did not fit within the British Association of Art Therapist definition or arts therapy (Lee et al., 2020). All four studies focused on individuals living with mild to moderate dementia. Two studies recruited participants from care facilities (Cheung et al., 2014; Mittelman and Papayannopoulou, 2018). One study recruited participants from a hospital and one study recruited participants from a pre-existing weekly singing group in the community. The number of people living with dementia-carer dyads ranged from three to fifty-eight. Two studies took place at a local arts centre (Bourne et al., 2019; Lee et al., 2020), one study was held in a church (Mittelman and Papayannopoulou, 2018) and one study was held in a dementia care facility (Cheung et al., 2014). All four studies involved weekly intervention sessions ranging from 6 to 10 weeks in duration. Each of the four studies employed different study designs: a randomised controlled trial (Cheung et al., 2014), pre-post pilot (Mittelman and Papayannopoulou, 2018), pre-post quasi-experimental (Bourne et al., 2019), and phenomenological study design (Lee et al., 2020). All four studies used mixed measures and analysis such as interviews, GDS (Yesavage et al., 1982), ROS, Modified Verbal Fluency Test (MVTF)(Chiu et al., 1997), and interpretive Phenomenological Analysis (IPA)(Smith et al., 2009) (Bourne et al., 2019; Cheung et al., 2014; Lee et al., 2020; Mittelman and Papayannopoulou, 2018).

3.14. Cognitive outcomes

Three of the four studies measured cognition in people living with dementia (Cheung et al., 2014; Lee et al., 2020; Mittelman and Papayannopoulou, 2018). Two studies (Cheung et al., 2014; Lee et al., 2020) reported improvements to memory. Two studies measured for changes in attention and engagement (Cheung et al., 2014; Lee et al.,

2020), and one (Lee et al., 2020) reported non-significant changes. Two studies reported improvements to communication and verbal fluency (Cheung et al., 2014; Mittelman and Papayannopoulou, 2018).

3.15. Well-being outcomes

All four studies measured well-being and QoL in people living with dementia (Bourne et al., 2019; Cheung et al., 2014; Lee et al., 2020; Mittelman and Papayannopoulou, 2018). Three of those studies also measured caregiver wellbeing (Bourne et al., 2019; Cheung et al., 2014; Lee et al., 2020; Mittelman and Papayannopoulou, 2018). All four studies reported improvements to well-being and QoL in people living with dementia, although in one study, people living with dementia showed statistically significant increases in composite happiness and optimism scores but not composite overall wellbeing (Bourne et al., 2019). One study reported significant improvements to caregiver self-esteem but not people living with dementia self-esteem (Mittelman and Papayannopoulou, 2018). Only one reported improvements to caregiver strain and the relationship between the PLWD and their carer (Lee et al., 2020).

3.16. Other forms of interventions

Seven studies assessed the impact of other arts and cultural intervention types for people living with dementia and their carers: heritage site visit and programme (n = 1) (Innes et al., 2021), heritage based activities (n = 1) (Li and Li, 2017), performance art (n = 1) (Kontos et al., 2017), dramatic performance viewing (n = 1) (Maeda et al., 2020), viewing of various types of performance (n = 1) (Loewy et al., 2019), theatre activity (n = 1) (van Dijk et al., 2011) and creative storytelling activity (n = 1) (Vigliotti et al., 2019). Two studies were delivered by trained facilitators (Innes et al., 2021; Vigliotti et al., 2019). Four studies were delivered by professional actors or artists (Kontos et al., 2017; Loewy et al., 2019; Maeda et al., 2020; van Dijk et al., 2011). One study was delivered by the researchers (Li and Li, 2017). Three studies did not specify dementia severity of participants (Innes et al., 2021; Kontos et al., 2017; van Dijk et al., 2011). Another three studies included individuals with any dementia severity (Li and Li, 2017; Loewy et al., 2019; Vigliotti et al., 2019), and one study focused only on individuals with mild to moderate dementia (Maeda et al., 2020). Participants were primarily recruited from dementia care facilities, but one study recruited participants from an existing heritage site programme (Innes et al., 2021), one study did not provide recruitment information (Loewy et al., 2019). The number of people living with dementia-carer dyads ranged from 20 to 103. Four studies took place in a dementia care facility (Kontos et al., 2017; Li and Li, 2017; van Dijk et al., 2011; Vigliotti et al., 2019). The other three studies took place at a heritage site (Innes et al., 2021), performance hall (Loewy et al., 2019) and in the dementia wing of a hospital (Maeda et al., 2020). Six studies included weekly intervention sessions lasting in duration between three and twelve months. One study did not specify if the intervention was multi-session or a single session intervention (Innes et al., 2021). Study designs included pre-post mixed methods design (Innes et al., 2021; Vigliotti et al., 2019), pre-post quasi-experimental design (Li and Li, 2017), pre-post 3-group quasi-experimental design (van Dijk et al., 2011), randomised controlled trial (Maeda et al., 2020), ethnographic observational (Loewy et al., 2019) and qualitative (Kontos et al., 2017) study designs. Five studies used both qualitative and quantitative measures such as interviews, Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) and QUALIDEM (Ettema et al., 2006) (Li and Li, 2017; Loewy et al., 2019; Maeda et al., 2020; van Dijk et al., 2011; Vigliotti et al., 2019). Two studies used only qualitative measures such as specifically designed mood questionnaires, video recordings and interviews (Innes et al., 2021; Kontos et al., 2017).

3.17. Cognitive outcomes

Six of the seven studies measured cognition in people living with dementia (Innes et al., 2021; Kontos et al., 2017; Li and Li, 2017; Maeda et al., 2020; van Dijk et al., 2011; Vigliotti et al., 2019). Two of the six studies reported significant improvements in overall cognitive status (Li and Li, 2017; Maeda et al., 2020). Three studies reported improvements in memory (Innes et al., 2021; van Dijk et al., 2011; Vigliotti et al., 2019). Another three studies reported improvements in attention and engagement of PLWD (Innes et al., 2021; van Dijk et al., 2011; Vigliotti et al., 2019). One study reported improvements related to humour including playfulness, ability to co-construct jokes and stories, and demonstrating understanding of humorous acts (Kontos et al., 2017).

3.18. Well-being outcomes

All seven studies measured well-being (Innes et al., 2021; Kontos et al., 2017; Li and Li, 2017; Loewy et al., 2019; Maeda et al., 2020; van Dijk et al., 2011; Vigliotti et al., 2019). Five studies reported positive changes to overall well-being and mood (Innes et al., 2021; Li and Li, 2017; Loewy et al., 2019; Maeda et al., 2020; van Dijk et al., 2011). Two studies reported significant reductions to neuropsychiatric symptoms in people living with dementia (Li and Li, 2017; Maeda et al., 2020). One study reported increased self-esteem for people living with dementia (Vigliotti et al., 2019). Four studies reported improvements in the relationship between the caregiver and people living with dementia and caregiver strain (Innes et al., 2021; Kontos et al., 2017; Loewy et al., 2019; van Dijk et al., 2011).

4. Discussion

This systematic review identified 34 articles investigating the impact of arts and culture interventions on the well-being and cognition of people living with dementia and their carers. Interventions included museum and gallery visits and activities, performances and performance art, heritage-based activities, storytelling, theatre activities, and music activities. Findings suggest that arts and culture interventions may have beneficial impacts on the well-being of both carers and people living with dementia, the relationship between carer and the person they care for, and improvements to cognitive skills in individuals living with dementia. All included types of arts and culture interventions reported improvements to the relationship quality between the person living with dementia and their carer. The majority of studies also reporting improvements to overall mood and well-being for people living with dementia and caregiver strain in carers. For people living with dementia the majority of studies reported improvements in cognitive domains of attention, engagement, memory and verbal fluency. Our findings are consistent with existing research on the impacts of arts and culture based interventions on the cognition and well-being for people with other forms of neurogenerative conditions (Barnish and Barran, 2020) and for caregivers of people living with other conditions (Kaimal et al., 2019). Our review adds to existing research by reporting well-being outcomes for both people living with dementia and carers, cognitive outcomes for people living with dementia and improvements to the relationship between the person living with dementia and their informal carer. To our knowledge this is the first review of its kind to explore the effects of a wide range of arts and culture interventions on the wellbeing and cognition of people living with dementia and caregiver strain within a single review; allowing for a greater understanding of the context of these interventions within the wider field of arts and health.

In qualitative measures, carers and people living with dementia cited that their improved relationship and communication could be attributed to participation in a shared activity outside of a caregiving situation, where they could enjoy the simple act of doing something together. People living with dementia and carers also stated the opportunity to socialise with other people living with dementia and carers as a

contributing factor to their improved well-being as it gave them the chance to discuss their experiences and exchange useful information. These qualitative findings suggest that stimulating activities and social interactions are potentially key mechanisms in understanding the cognitive and well-being benefits that arts and culture interventions have to offer. Existing research supports that arts activities that are both mentally stimulating and encourage social interactions are essential to the well-being and cognition of individuals in the general public and people living with dementia (Bosco et al., 2019; Camic et al., 2016; While, 2020).

4.1. Evidence from randomised controlled trials

Only five randomized control trials fit inclusion criteria for this review. Detailed information about these studies can be found in Table 1 and information on the quality of these studies can be found in Appendix A. All five RCTs utilized different intervention types: immersive reminiscence in a museum (Kirk et al., 2018), museum visit and art activity (Schall et al., 2017), art making activity (Richards et al., 2019), music with movement activity (Cheung et al., 2014) and a dramatic performance viewing (Maeda et al., 2020). The majority of these studies reported improvements to well-being and cognition for people living with dementia(Cheung et al., 2014; Kirk et al., 2018; Maeda et al., 2020). One reported improvements to well-being in people living with dementia and cares but not cognition in people living with dementia (Schall et al., 2017) and another did not measure well-being and reported no cognitive improvements in people living with dementia(Kirk et al., 2018).

4.2. Implications and recommendations for future research

Given the increasing prevalence of dementia, the benefits of arts and culture interventions for people living with dementia and their informal caregivers must be explored further. The findings of the current review suggest that arts and culture interventions offer benefits for people living with dementia and their carers. The majority of included studies reported the positive effects of arts and culture interventions on the well-being for people living with dementia and their carers. These findings are consisted with broader existing research on the benefits of the arts on health and well-being. Arts and health can help in a variety of health and well-being conditions including ageing, long-term conditions, loneliness, recovery and mental health; even providing relief to carers, health services and social care services (Marmot et al., 2017).

This review indicates apparent gaps in the types of arts and culture interventions offered as there were little to no interventions in for some types of arts and culture such as dance, literature or heritage sites. This review also indicates an imbalance in interventions for different severity levels of dementia. Seventeen of the included thirty-four studies focused only on participants with dementia in the mild to moderate range and in the nine studies that included people living with any dementia severity, most of the participants were living with dementia in the mild to moderate range. Five studies did not specify dementia severity of the participants living with dementia. Only one study focused on individuals with moderate to severe dementia (Sauer et al., 2016). Findings from one study suggest that people living with dementia in the mild to moderate range might experience a greater increase in self-esteem, attention/interest, pleasure and improved cognitive outcomes such as reminiscence than those in the in the moderate to severe range (Vigliotti et al., 2019). It would be informative to understand the differences, if any, in the impact of these interventions on people at different stages of dementia and how benefits may change with dementia severity level. We recommend that future studies aim to have balanced participation of people living with all stages of dementia and compare impacts across severity levels.

More than half of the included studies took place in a museum or gallery setting, studies that involved a comprehensive range of intervention activities such as going to a heritage site (Innes et al., 2021), viewing a performance (Loewy et al., 2019) and interactive theatre activity (van Dijk et al., 2011) suggested that alternative forms of arts and culture interventions can also provide benefits for people living with dementia and their carers. Only seven studies were delivered at the participants place of residence, suggesting there is a lack of research in out-reach programming for people living with dementia who are unable to travel to a secondary location. Findings from studies suggest that neuropsychiatric symptoms that negatively impact well-being such as agitation and delusions might significantly decrease for people living with dementia when interventions are delivered at their place of residence (Li and Li, 2017; Maeda et al., 2020) compared to a secondary location like a museum (Schall et al., 2017). Additional interventions involving a range of activities separate from visual art and museums and delivered at the participants place of residence should be studied further to explore their potential benefits. Further small-scale studies, particularly in museum or gallery settings, will not add to the knowledge base. Larger studies are needed to fully understand both the effects of these interventions on people living with dementia and their caregivers as well as any differences in the effects of type of arts and culture intervention may have.

Only eight of these studies employed follow-up measurements ranging from one month to six months follow-up. These studies primarily reported continued positive effects on well-being and cognition for people living with dementia and improvements to carer well-being at follow-up. However, given the limited number of studies that conducted follow-up and the range of follow-up times our confidence in the long-term effects of these interventions is limited. Future studies should provide multiple follow-up points over at least six months so that the long-term effects of arts and culture interventions for people living with dementia and their carers can be better understood.

Only one study involved people with lived experience of dementia in the designing of the intervention. Public involvement in health and social care matter is essential to understanding and improving health and well-being (Government, 2012). It would be beneficial to use personal and public involvement (PPI) for future or co-produce interventions in the future to better understand the needs and perspectives of people living with dementia and their carers.

As many studies reported benefits of socialisation and shared activities through qualitative measurements, future studies could benefit from utilising intervention specific measurements to measure outcomes related directly to the aims of the intervention as well as standardised measures such as the MMSE and BI to provide a bespoke understanding of intervention benefits. We also recommend conducting supplementary studies that further explore improvements to negative feelings and emotions, especially measurements for caregiver strain.

Arts and culture interventions for people living with dementia and their carers are varied and complex; a more systematic approach is needed to develop them further and evaluate them. To aid in collecting statistically significant data, we recommend employing larger sample sizes, including a range of participants in various stages of dementia, determining effect sizes of outcome measures to test efficiency and, given the varied study designs found in this review, we recommend using randomised controlled designs whenever possible to establish effectiveness in a rigorous manner and compare the intervention outcomes to control groups. We also recommend that future studies include a clear and detailed description of the intervention, delivery modes, and any intervention-specific training that practitioners delivering the programme receive, as this information was not provided in the majority of included studies and might help to identify and understand the mechanisms of action by which the intervention might achieve it's intended outcomes. When measuring mental health and well-being outcomes, future studies should collect information on any relevant medication prescriptions meant to alter mood, such as antidepressants, as these medications might impact outcome results. We recommend that future studies use arts and health based frameworks such as the INNATE framework to support the design, implementation and evaluation of arts

and culture interventions for people living with dementia (Warran et al., 2022). The use of frameworks like INNATE or the WHO's new 'Guide to evaluating behaviourally and culturally informed health interventions in complex settings,' would help to design and evaluate more structured studies and provide a deeper understanding of the mechanisms of change these arts and culture interventions have for people living with dementia (Scott et al., 2022).

4.3. Strengths and limitations of the review

To our knowledge, this is the first review of its kind to assess a broad range of arts and culture interventions currently used within dementia research. We had an inclusive search strategy in five databases, screening and quality rating were carried out independently by two raters and we used robust quality assessment tools.

A meta-analysis was not possible due to the heterogeneity of data. However, the qualitative data provided was sufficient to enable a narrative synthesis that informed recommendations for further research. Limitations of the review were that we did not include search terms for types of interventions or cognition which could have meant we omitted some studies. However, as dementia is a neurocognitive disorder, cognitive outcomes were retrieved in searches. We did search for arts and heritage settings and used other reviews and reference lists to identify more possible studies for inclusion. The limitations of included studies were primarily their inconsistent outcome measures and reporting which affected the confidence of conclusions made in this review. However, we acknowledge that arts and culture interventions for people living with dementia and their informal carers can be challenging to conduct and evaluate due to the complex nature of dementia and challenges associated with working with this population. However, if there is evidence that an intervention can provide improvements to mental health or cognitive skills, then it should be encouraged.

5. Conclusion

This narrative synthesis systematic review assessed 34 articles that used art and culture interventions to improve wellbeing and/or cognition for people living with dementia and the wellbeing of their informal caregivers. Our findings suggest that participation in arts and culture interventions improved well-being, QOL, and cognitive skills and functions. Evidence from randomised controlled trials shows that arts and culture interventions may be associated with improvements to cognition and well-being, however these studies were relatively small. Larger scale randomised controlled trials would need to be conducted to provide confidence in the effects of different types of ats and culture interventions for people living with dementia. The most listed positive effects from qualitative measures of these interventions were improved well-being for people living with dementia and carers, improved communication, and socialisation in people living with dementia and improved person living with dementia-carer relationships. Expanding participation to those living with moderate to severe dementia and their informal carers, larger and additional randomised controlled trials and more robust assessment of outcomes is needed to more thoroughly examine the effects of these interventions.

Data Availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101793.

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The development of a novel Wellness Assessment Instrument and its use in the assessment of wellness status in patients with chronic obstructive pulmonary disease

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chronic obstructive pulmonary disease; wellness status; health status; spirituality; psychology

Abstract

Aims: Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disorder that affects health outcomes on multiple levels including overall wellbeing. More specifically, factors such as spiritual wellbeing, and psychological, mental and motivational status which may be at least as important as others, have been rarely studied. This article reports the method of validating a new wellness assessment questionnaire and the status of several wellness domains in patients with COPD.

Methods: The study consisted of two phases: first, the development of a new Wellness Questionnaire with the help of focus groups; second, the validation and use of the questionnaire in a cohort of patients with COPD. For focus groups, healthy people ⩾45 years of age with no known comorbidity as well as people with a clinical diagnosis of COPD were invited to participate in the study.

Results: Thematic analysis of findings from focus groups and original cohort respondents highlighted some factors that appear to influence wellness status. Five domains were explored as potential markers of wellness in patients with COPD. Quantitative analysis with Spearman correlation demonstrated a significant correlation between Physical/Personal Wellness and other markers of COPD progression such as Global Initiative Obstructive Lung Disease (GOLD; 0.006), force expiratory volume in 1 s (FEV1%; 0.01), health-related quality of life (0.009), multidimensional BOD score and quartile (0.003 and 0.02).

Conclusion: The findings suggest that a combination of personal, physical, emotional, mental and other psychological factors is responsible for negative COPD outcomes. While there is a need to validate this new wellness questionnaire in further research, it incorporates new markers of wellness that could benefit management of COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex chronic disorder and is one of the most prevalent diseases worldwide. It is also predicted to be the third most common cause of death by 2030.[1] The most common symptom these patients exhibit is shortness of breath that significantly impair COPD outcomes. One of the main goals in managing these patients is to maintain a good quality of life and overall 'wellness' for those affected.[2] However, in order to achieve and maintain 'wellness', clinicians are faced with the challenge of selecting a reliable tool that effectively assesses the severity of the disease and measures its effect on improving the patient's overall quality of life. Studies suggest that there is a close link between breathing and wellbeing.[3,4] Ardell[5,6] suggested that 'Breathing

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plays a role in long-term well-being' and according to Japanese proverb 'Cheerfulness is the very flower of health'. In other words, 'Health' has a general superficial meaning that means a person is in a disease-free state. Absence of current disease is no guarantee of a perfect disease-free future. There may be some hidden or unseen aspects of an individual's life that may influence health and wellbeing. These include social interaction, sense of self-responsibility, mental fitness or a stress-free mind which would otherwise interfere with sleep, daily activities and appetite[7] and thus contribute to slowly progressive conditions like hypertension, diabetes, anxiety and depression.[7] Wellness can be regarded as a mental approach related to the lifestyle a person adopts or mental attitude that at the highest level of wellbeing can act as a placebo effect.[8] Wellness involves an integration of body, soul and mind and a belief in health.[9] Daily personal, social and emotional activities may have an impact on illness progression and recovery in both positive and negative ways.[10] Therefore, an assessment of wellness in patients with COPD has the potential to enhance disease outcomes. This is needed in the event of any chronic illness to develop awareness, energy and knowledge so that individuals can cope more easily with the realization that there may be no endpoint before death. Thus, it has the advantage of maintaining hope and encouraging a healthy lifestyle to avoid disease complications. Wellness involves an integration of body, soul and mind and a belief in health.[9] It enables a person to realize that everything we observe, think, perform and feel has a major impact on our state of health and state of wellbeing.

COPD is a complex condition involving multiple clinical manifestations that significantly impair functional, physiological and psychological health. Living with COPD requires people to manage disease-related symptoms in order to participate in the activities of daily life. It has been suggested that a patient's health-related quality of life (HRQoL) is linked to COPD outcomes[11] which may mean that an improvement in HRQoL could lead to improvements in other COPD-related measures. Mindfulness practice is an intervention that has been shown to reduce symptoms of chronic disease and to improve accurate symptom assessment, both of which could result in improved disease management and increased wellness for people with COPD.[12] Wellness is a measure of physical, psychological and spiritual wellbeing that may provide a concealed picture of health status and may help in understanding all the factors responsible for supporting and improving health status.[13] For this reason, it seemed worthwhile to assess the psychological status and wellbeing of individuals with COPD.

Therefore, an assessment of wellness in patients with COPD potentially enhances disease outcomes and this study has tried to explore this phenomenon in the study participants. To date, no study has examined how wellness status can be assessed in patients with COPD or whether wellness is related to health measures in a COPD population. Thus, the purpose of this research was to design a questionnaire suitable for assessing wellness in persons with COPD and to determine any association of wellness with other COPD outcome measures.

METHODS

An initial objective was to design a suitable wellness questionnaire; the second objective was the identification and selection of patients with COPD to engage with the questionnaire in a pilot study. To fulfil the first objective, several existing wellness questionnaires were critically reviewed to identify generally accepted wellness-related domains, then the most suitable questions used to assess wellness and from these a draft questionnaire was designed. The feasibility and acceptability of questionnaires to assess several different wellness measures for patients with COPD was investigated using focus groups.

After getting approval from the Ethics Committee of Sunderland University, three community focus groups from Age Concern and Breathe Easy in both Sunderland and South Tyneside were approached to ascertain views about the concept of wellness and the questionnaire itself.

Following further ethical approval by the NHS (National Health Services), LREC (Local research ethical committee) and the University of Sunderland Ethical Committee, the questionnaires produced after consultation with the community focus groups were sent to COPD study participants by post, together with a prepaid addressed envelope, an explanatory letter, a consent form to confirm the voluntary nature of participation in the study, an information sheet about how to complete the questionnaire and contact details in case there were any concerns to discuss. If necessary, a home visit or hospital appointment would be made at the patient's request.

The discussion was started with a question to seek participants' views on how to assess wellness status as opposed to health status. Of importance was the ease of comprehension and the likely relevance of questions to the target population of patients with COPD with mild, moderate and severe manifestations of the disease. Following feedback from the focus groups, the questionnaire was modified and finalized (Figure 1).

Analysis of focus group findings was carried out using (a) audio transcripts, (2) handwritten notes by the researcher and (3) thematic analysis.

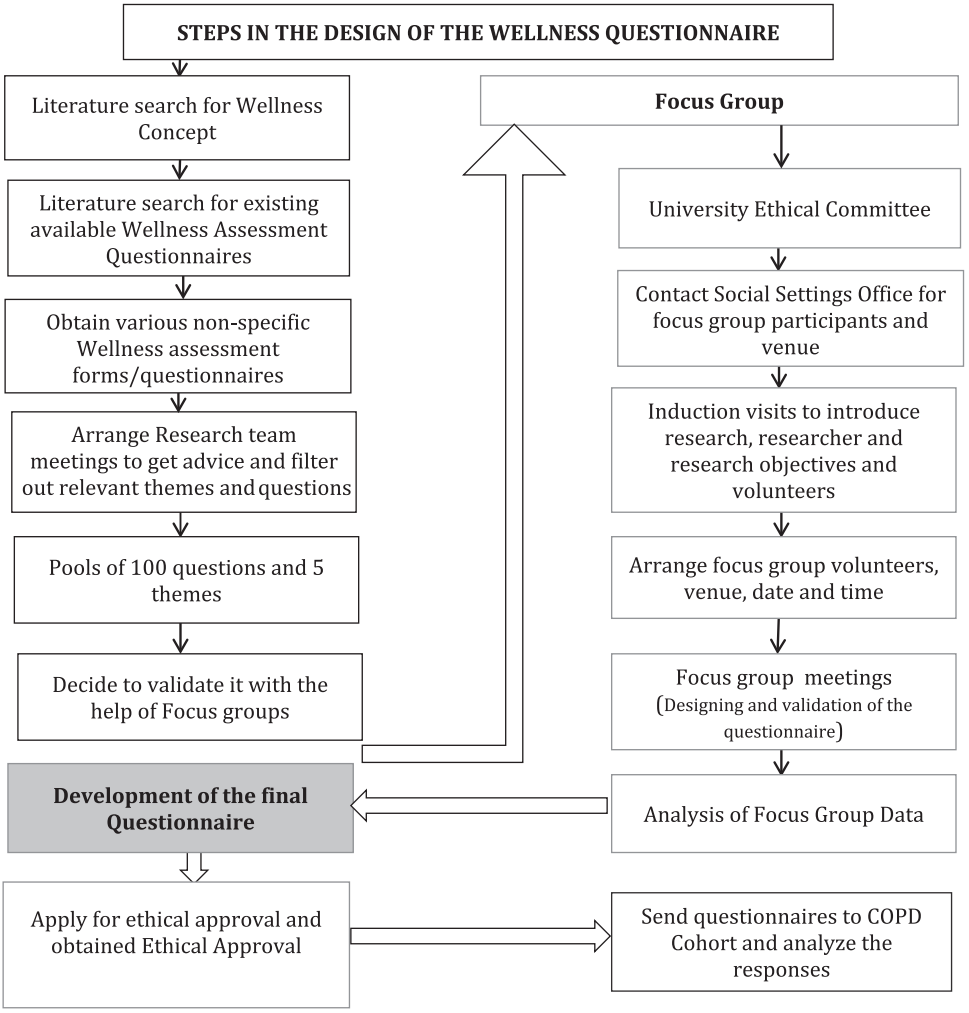
All quantitative data were assessed using SPSS (IBM version 22, Inc. UK). Baseline measures were evaluated using Student's *t*-test for differences between groups. Pearson product moment correlation coefficient (Pearson's *r*) was used to analyse the correlation between wellness domains and COPD outcomes including lung functions as measured by FEV1% predicted, degree of breathlessness by Medical Research Council (MRC) dyspnoea score, severity of COPD by modified Gold staging and HRQoL by St. George's Respiratory Questionnaire (SGRQ) scores. *p* value of $\leqslant .05$ was considered as statistically significant.

RESULTS

All participants were divided into three focus groups (F1, F2, F3) on the basis of

Figure 1

Schematic representation of the steps taken to design a wellness questionnaire suitable for study participants.



induction and session venues. Number of participants in group F1 were 8, 6 in group F2 and 6 in group F3. Several emergent themes were explored. There were no set criteria for inclusion or exclusion of participants. Researchers ensured inclusion of participants who were demographically similar to those with COPD and in good health. Figure 2 represents the steps of focus group analysis.

The demographic characteristics of the participants of focus groups F1, F2 and F3 are presented in Table 1. The participants in all focus groups were Caucasian. Figure 3 is a bar chart representing the frequency of different words that the participants used in relation to wellness assessment markers during the focus group sessions. Table 2 shows the key words used by the participants during all focus group discussions.

Different sources of stresses that occupied the minds of participants that were believed to interfere with health were mentioned, although there was no specific reference to symptoms or consequences of disease.

After critical analysis of the literature, a questionnaire was initially derived consisting of five potential themes/domains that are appropriate to assess wellness status in patients with COPD. These were Personal, Self-Responsibility, Daily Stress, Stress Management and Physical Wellness.

The focus groups also gave views on other aspects of the questionnaire. These include the question content and wording, response format, question sequence and questionnaire layout. A consensus was found regarding different aspects of the questionnaire across focus group members suggesting the questionnaire to have been well structured, easy to understand and to cover a range of health and wellbeing-related issues.

Validation of wellness questionnaire in COPD cohort

The health characteristics of the participants are shown in Table 3. Results show that respondents of the wellness questionnaire had severe

Figure 2

Stages of focus group analysis.

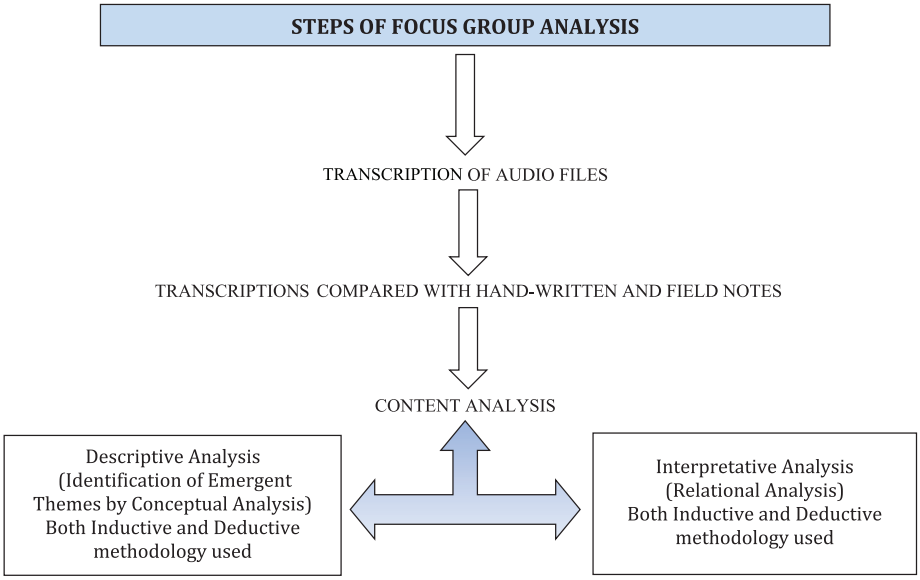


Table 1

Characteristics of focus group participants and the session venues

Characteristics	Focus group 1 (F1)	Focus group 2 (F2)	Focus group (F3)
Source	Age Concern, Sunderland	Breath Easy group, Sunderland	Breath Easy group, Sunderland
Induction venue	Nursing Homes Hendon and Seaburn	Primary Care Centre, Sunderland	St. Gregory's RC Church, South Shields
Session venue	Age Concern, Sunderland	Primary Care Centre, Sunderland	South Tyneside Hospital, South Shields
Number of respondents (R)	8	6	6
Gender (M/F)	1/7	5/1	3/3
Age range	45-75	60-75	60-75
Health issues	None	COPD, emphysema, bronchiectasis	COPD, emphysema, bronchiectasis
Motivation of participants	Enthusiastic, highly motivated and enthusiastic	Enthusiastic, highly motivated and actively took part in the discussion	All were vocal, highly motivated and interested to discuss the questionnaire therefore actively took part in the discussion

COPD: chronic obstructive pulmonary disease

manifestation of their clinical condition as indicated by their FEV1% predicted of 45.4 ± 19.2 with mean MRC score of 3, but better health status with total SGRQ score of 44.1 ± 19.6.

The final questionnaire was given to the participants and the cohort was asked to mark whether the statement applied to them rarely, sometimes, most of the time or always.

Quantitative analysis (Table 4) using Spearman correlation indicated that significant correlations were found between Physical/Personal Wellness and other markers of COPD progression such

Figure 3

Frequency of different words that the participants used.

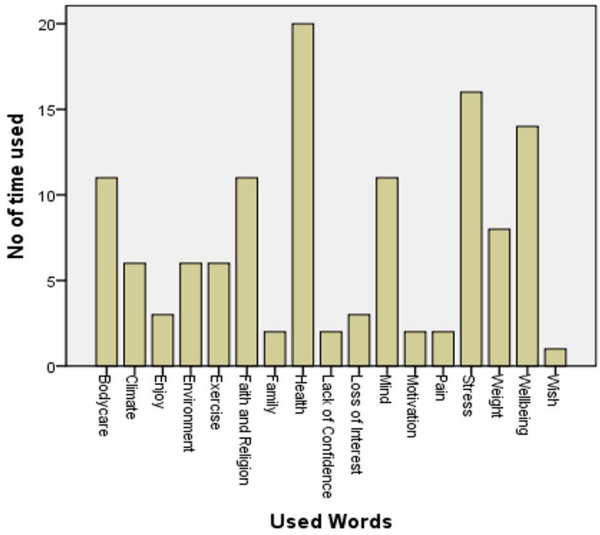


Table 2

Themes generated from focus group sessions

Wellness-related issues/emergent themes	Key words used
Stress factors	Stress due to family Stress due to finance Lack of exercise Age Lose weight Weight gain Diet Hate drugs Body pain Loss of interest
Environment	Germ-free environment Healthy and clean
Spirituality	Meditation Church God Prayers Many people go to church

as GOLD (0.006), FEV1% (0.01), HRQoL (0.009), multidimensional BOD (**B**ody Mass Index, airflow **O**bstruction, MRC **D**yspnoea Score) score and quartile (0.003 and 0.02) suggesting that wellness is related to disease progression and may have an impact on it.

Concept of wellness and the need to assess wellness

When asked to explain wellness in one phrase, focus group participants used different terms such as 'interesting term', 'psychological picture', 'pain free body is wellness' and 'more good health than a basic mind'. An attempt was made to combine all of these terms to form an opinion-based definition of wellness:

> *A psychological state with peace of mind and a pain free state of a body in addition to good physical health.*

Focus group members perceived that each dimension of wellness has to work in harmony with the others for optimal health and wellness to be achieved. The focus group participants provided insight during the sessions into previously unidentified wellness domains that eventually helped to improve accuracy and design of the developed questionnaire. When asked if they were sure they really understood the concept of wellness, all the focus group participants nodded in agreement. It was apparent that they were aware of the term 'Wellness' as they used phrases such as 'oh definitely' and 'interesting term but not a common one' ...

Themes emerging from focus group sessions

Stress

On the basis of focus group responses, members experienced different forms of stress as shown in Table 5. All of these appeared to play a major role in overall health and wellbeing.

The % a person agreed with each of five options for each statement of each domain (5 domains; 10 statements in each domain; 50 statements in total). The responses with a high level of agreement were found and are presented as percentages in Table 6. The responses were presented in the form of percentages. Table 6 indicates that majority of COPD subjects showed bipolar variation in their responses to the wellness questionnaire which means they either marked the first two options of the Likert-type scale (rarely or sometimes) or the last two options (most of the time/always) in response to a written statement of the questionnaire that was somehow applicable to the patient's condition. For example, all patients responded as either 'most of the time' or 'Always' against the statement 'I experience moodiness/angry outbursts because of my illness'.

Table 3

Health characteristics of the COPD respondents (*n* = 27)

Age (years)		68.8 ± 9.3
Gender (M/F)	Male	15 (56%)
	Female	12 (44%)
Pack years (years)		39.02 ± 17.91
BMI (kg/m^2)		27.61 ± 5.72
FEV1 % predicted		45.40 ± 19.20
MRC (1–5)		3.21 ± 1.35
GOLD (1–4)		2.75 ± 0.90
SGRQ Total%		44.14 ± 19.61

BMI: body mass index; FEV1: force expiratory volume in 1 s; MRC: Medical Research Council Scale; GOLD: Global Initiative Obstructive Lung Disease; SGRQ: St. George's Respiratory Questionnaire.
Data are presented as mean ± SD; *p*-value = assessed by Mann-Whitney U Test.

Table 4

Relationship of wellness domains with COPD markers

Wellness domains	COPD markers of progression	*p* value
Personal/physical wellness	GOLD stage	.006
	SGRQ score	.009
	FEV1 %	.01
	MRC	.03
	BMI	.02
Emotional wellness		Not significant
Self-responsibility-related wellness		Not significant
Mental wellness		Not significant
Spiritual wellness		Not significant
Total wellness		Not significant

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative Obstructive Lung Disease; SGRQ: St. George's Respiratory Questionnaire; FEV1: force expiratory volume in 1 s; MRC: Medical Research Council Scale; BMI: body mass index.

Spirituality

Spirituality was a theme that emerged in the first focus group discussion. It had not initially been included in a first draft of the questionnaire as the literature did not indicate that this was a component of wellness or health. However, when the group was asked if there was any other issue that could be incorporated in the questionnaire to assess wellness, three female members of the group initiated a discussion about whether spirituality could be considered as a wellness indicator and this idea was supported by other members. None of the participants in both focus groups objected to the inclusion of the spirituality section in the wellness assessment.

The qualitative analysis of wellness status in patients with COPD showed that the spiritual section of wellness status was of interest to the respondents, with comments such as the following being made:

> *Going to church gives me feeling of peace*
> *God is not a whim.*

However, one participant 'found the spirituality section very difficult'.

As a result of such statements, the questionnaire was revised to incorporate the potential importance of exploring the influence of spirituality on disease management.

DISCUSSION

Wellness is usually defined as being in a state of good physical and mental health and appears to be understood differently depending on the circumstances and lifestyle-related problems that an individual face. Each person's definition of wellness will largely depend on how they perceive, assess and manage their needs and life circumstance or events. In this study, opinion-based definition of wellness was derived from focus group discussions. This was followed by the development and validation of a new questionnaire; the Sunderland Respiratory Wellness Questionnaire

Table 5

Summary of the emergent factors that contribute to wellness status

Wellness-related issues/ emergent themes	Key words used
Stress factors	Stress due to family, disturbed sleep, diet, and other health problems. Lack of exercise
Environment	No smoke-free environment, dust, pollutants, clean air, no chest complaint since moved from one place to another, pubs are clean, no smoking in the family, never smoke
Spirituality	Church, feeling of peace, God, helping others, difficult to respond

(SRWQ), believed to be the first questionnaire to assess wellness in patients with COPD.

Focus group discussions led to the development of the following definition of wellness: 'A psychological state with peace of mind and a pain free state of a body in addition to good physical health'. This is consistent with the definition 'A multidimensional state of being describing the existence of positive health in an individual as exemplified by quality of life and a sense of well-being'.[14]

This study showed that, in some circumstances, attempts made to minimize stress formed the precipitating or aggravating stress factor. It therefore seems possible that, by assessing the influence of patients' wellbeing on COPD outcomes, carers and healthcare professionals may be helped to plan better strategies and to find better solutions to problems in the future.

Because of the interest in spirituality and wellness shown in this study, further research is needed to explore possible links between spirituality and COPD outcomes. Many feel that good health is the just reward of living a good life, and illness is the punishment for one's spiritual shortcomings. This view has been around since mankind has sought the answers to why some become ill or suffer misfortune. It is possible that the terminal nature of COPD makes some sufferers more spiritually conscious. Alternatively, it is possible that the participants were more spiritually aware than the population at large. As some members of the focus group belonged to a Christian Church group, it is possible that this led to a concern about spirituality, which then became incorporated into the questionnaire. It is therefore possible that any link demonstrated between spiritual status and health/wellbeing is restricted to those who already have a faith.[15,16]

To date, the majority of indices developed for the evaluation of COPD have concentrated on physical, physiological and biochemical measures.[17] However, a person's attitude towards their illness can often impact upon the outcome in terms of morbidity and mortality. Also, in any evaluation of disease progression, it may therefore be necessary to include an assessment index measure of 'wellness' or their mental attitude towards their illness.[18,19]

This study also attempted to explore the deeper picture of the overall health status in these patients with the help of a newly developed 'Sunderland Respiratory Wellness Questionnaire'. This suggests the need for its use in patients with COPD to get a deeper picture of the overall health and potential impact on outcome, better management and prognosis. In addition, the psychological/ wellness status enhances the assessment of overall health status incorporating general, physical and mental health status, which together improves overall health outcomes.

The key factors that the patients felt impacted upon their wellness include stress factors, self-care and spirituality.

From the analysis of focus groups, written comments from patients with COPD and responses in the wellness questionnaire, a variety of stress factors have been identified as markers that influence COPD outcomes. These include self-induced stress, nutritional stress, physical, emotional, spiritual, mental and environmental stress.

In addition to stress factors, the qualitative study has also identified other factors that may further impact upon health and general wellbeing in patients with COPD. These include hope and positive attitude, self-care and personal beliefs.

All these factors could be useful and while they do not need new treatment interventions, they require support from family, friends, relatives, healthcare workers and society. In this regard, the most vital need is to determine a patient's requirements, needs, views and resources that collectively help these patients to be well informed. This in turn can motivate patients and keep their attitude positive towards the maintenance of good health.

For example, when a patient is under stress, they tend to ignore healthy/ regular meals and thus may create further stress in the long run. Therefore, extra support may be needed to make food choices. Furthermore, having COPD may cause a gradual variation and deterioration not only in their lifestyle but also in their relationship with family members, relatives, spouse, siblings and friends. It is believed that by sharing their feelings and concerns, perception of their illness may be improved resulting in the positive energy needed to overcome disease consequences. In addition, the assessment of wellness may also enhance the assessment of health status in these patients which in turn can lead to an improvement in their quality of life.

Table 6

Records of the participant who scored each statement (3 – being agreed or 4 – strongly agree)

Wellness domains	High wellness	Low wellness
Personal/physical wellness	I have good appetite and enjoy my food (89%)	I rarely engage in vigorous exercises (71%)
	My liquid intake is adequate (93.3%)	I have negative or critical feelings about myself (52%)
Emotional wellness	I am flexible and adopt or adjust to change in a positive way (85%)	I use alcohol as a means of helping me forget my problems (90%)
		I experience moodiness/angry outburst because of my illness (100%)
		I assess my current state of health and stress level on daily basis rarely (78%)
Self-responsibility-related wellness	I believe my life is in my hands and I control it (94%)	I am aware that I am responsible for every aspect of my life (58%)
	I believe the way I live is important in improving my health (93%)	I take a variety of supplements or alternative therapy to help maintain my health rarely (84%)
	I believe I am a major force in determining my rate of recovery from an illness (94%)	
	I try to perform at least one good deed every day (74%)	
	I am keen to maintain a healthy lifestyle and healthy diet (80%)	
Mental wellness	I have good sense of wellbeing about my health (70%)	I feel tired or have low energy (84%)
	I manage my time rather than time managing me (84%)	I am stressed by my family (90%)
		I am stressed because of my finances (89%)
		I am stressed because of house work (88%)
		I feel stressed when I go shopping (95%)
		I feel generally stressed by my bowel habits (100%)
		I am stressed by having to rely on others (84%)
Spirituality	I believe life is a precious gift (90%)	I rarely go to church or other place of worship (85%)
	I engage in acts of caring and good will without expecting something in return (85%)	Practicing my faith rarely occupies an important part in my life (89%)
		I do not pray for better health (82%)

Therefore, the management of COPD should be carried out on an individual basis considering personal and social factors that interfere with the progression of this disease. How the healthcare workers approach these individuals is also an important factor that needs consideration. For example, general instruction to 'stop smoking' is the key target by clinicians to improve COPD-related health outcomes. However, attention should also be given on the contributing factors that prevent them from stopping smoking, for example, health-related stress factors, social factors or attitude.

This study has combined quantitative and qualitative research in the development of new methods for the evaluation of patients with COPD and management of their care. While further research is needed to validate this new questionnaire, initial study results provide a starting point which will enable healthcare practitioners to evaluate the wellness of individual patients and to devise appropriate care packages that not only manage their physical symptoms but also support their 'wellness'.

Combining qualitative and quantitative measures

Many studies into the development of indices of COPD progression have solely focused on physical measures.[20,21] Few have attempted to assess mental status and its association with COPD progression[22,23] and health status.[24] However, to date, no study brings together an assessment of a patient's physical symptoms and a measure of their mental attitude (and the factors that impact upon it) so that both aspects can be considered in the long-term management of the illness. This study explores this phenomenon for the first time.

In all evaluations of disease progression, there is a need to evaluate both physical factors together with 'wellness' and attitude. Management of health and the outcome of disease are a mixture of both, and a multidisciplinary index should assess both measures. This means a blending of quantitative and qualitative methods. In practice, this does not generally occur as studies are either carried out by physicians/clinicians or social scientists.

This study benefitted from support from both types of expertise and it has illustrated the need to merge both types of research in the development of future indices for the management of COPD.

CONCLUSION

This study needs to be considered as a unique addition to the literature with respect to the identification of new markers of wellness status for the improvement in overall health and wellbeing in these patients. This could guide physicians to identify areas for self-care and help them to promote a self-management approach to managing COPD. The findings suggest that the combination of personal, physical, emotional, mental and other psychological factors is responsible for negative COPD outcomes which further deteriorates its progression. Further research is needed to assess the utilization of this tool in a large group of patients with a range of disease severity. There is a need to further validate the Wellness questionnaire, its reproducibility and its correlation with other tools that are being utilized to assess health status and to explore wellness as a concept in other patients with COPD from other ethnic groups.

Future research should focus on how self-management skills can be incorporated formally into medical care. In addition to offering suggestions on how clinicians may be instrumental in improving self-management behaviour in patients with COPD, and thereby improve care outcomes, we highlight the importance of gaining insight into the perceptions of patients of their own situation and incorporating a respect for patient perspectives into the philosophy of care.

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AUTHOR CONTRIBUTIONS

All authors have contributed to writing and revising the manuscript.

CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

ETHICAL APPROVAL

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

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The study protocol (08/Q0904/43), including its consent form and survey template, was reviewed through Local Research Ethics Committees, University of Sunderland and Sunderland Royal Hospital. The IRB granted a Waiver of Written Documentation of Consent on the grounds that this study is a postal survey that does not include direct identifiers, there are no physical risks imposed by this study, does not involve procedures for which written document of consent process is normally required outside of the research context and the research is not FDA regulated.

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RESEARCH Open Access

Evaluation of breastfeeding and infant feeding attitudes among syrian refugees in Turkey: observations of Syrian healthcare workers

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Abstract

Background The influx of Syrian refugees into Turkey has highlighted the importance of supporting breastfeeding practices among this vulnerable population. We aimed to evaluate the breastfeeding and infant feeding attitudes of Syrian mothers based on the observations of Syrian healthcare workers (HCWs).

Methods An online form including 31 questions was prepared in Turkish, Arabic, and English languages and distributed to HCWs, working in refugee health centers via e-mail, WhatsApp, or text message with the help of Ministry of Health in Turkey between January 2020 and March 2020. The questions were about HCWs' characteristics (occupation, region of employment, duration of employment, participation in breastfeeding counseling course) and about HCWs' observations of Syrian mothers' breastfeeding and infant feeding practices.

Results A total of 876 HCWs were included in the study; about 37.3% were physicians. Only 40.0% of HCWs reported that babies were predominantly fed with breast milk in the first three days after birth, 45.2% of HCWs indicated that mothers typically used sugary water as a prelacteal food, and 30.5% believed that breastfeeding was discontinued before 12 months. The main barriers to breastfeeding identified by HCWs included the lack of education, mental and physical health issues in the mother, food insecurity, low income, inadequate housing, lack of family planning, sociocultural environment, and limited access to quality health services. For complementary feeding, 28.0% of HCWs stated early introduction and 7.4% remarked delayed. HCWs believed grains, fruits and vegetables, and dairy products as top three foods for starting complementary food (59.5%, 47.8%, and 30.3% respectively). Healthcare challenges of Syrian pregnant and lactating mothers were reported to be associated primarily with "food, finance, and housing difficulties", low maternal education, and cultural and environmental issues. HCWs recommended various solutions, such as supporting breastfeeding, offering nutrition and health support, promoting family planning, improving healthcare systems through legislation, and addressing cultural barriers.

Conclusions To address breastfeeding issues among Syrian mothers, it is crucial to provide breastfeeding training to both HCWs and mothers. Expanding interventions that support breastfeeding-friendly practices, including community support and food aid for breastfeeding mothers, should also be considered to address the social determinants of breastfeeding.

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Keywords Syrian refugees, Breastfeeding, Social determinants of health, Breastfeeding-friendly, Turkey

Background

Given the importance of breastfeeding for both mothers and infants, World Health Organization (WHO) recommends initiating breastfeeding in the first hour, exclusive breastfeeding for the first six months of life, followed by continued breastfeeding alongside complementary foods for up to two years and beyond [1, 2]. This recommendation is particularly crucial in high-risk situations as disasters or migration, where access to clean water is limited and the risk of infection is high, making artificial feeding more dangerous for child health and survival [3].

Since the onset of the Syrian war in 2011, Turkey has become the host country for a significant number of Syrian refugees due to its proximity to Syria. As of 2022, there are over 3.5 million Syrian refugees under temporary protection in Turkey [4]. Although breastfeeding is a fundamental right of the child, many factors determine the initiation and continuation of breastfeeding. Forced migration is known to have a negative impact on breastfeeding practices [5, 6]. Despite having a positive attitude towards breastfeeding, many Syrian refugee mothers have a shorter duration of breastfeeding, with most discontinuing before the child reaches 12 months [7, 8].

To address the healthcare needs of Syrian refugees, the SIHHAT project, funded by the European Union, has been implemented in Turkey. This project involves the establishment and expansion of refugee health centers (RHCs) that provide primary healthcare services to Syrian refugees under temporary protection. Syrian healthcare workers, including physicians and nurses, are employed in these centers [9].

This study aims to explore the observations and recommendations of Syrian healthcare workers (HCWs) working in RHCs regarding breastfeeding practices and feeding difficulties faced by Syrian refugee infants according to HCWs' job and working region. By obtaining insights from these HCWs, it is possible to identify key areas for intervention and support to improve breastfeeding rates and address the challenges specific to this vulnerable population.

Methods

Study design

The study design of this research was a descriptive study conducted between January 2020 and March 2020 in collaboration with the Ministry of Health of Turkey and Hacettepe University. The study aimed to gather information about the observations of HCWs regarding breastfeeding and the nutritional status of Syrian refugee infants living in Turkey.

Study population

The population of the study consisted of Syrian physicians and nurses (midwives were also considered in this category) working in RHCs in Turkey. HCWs of other nationalities and non-medical staff (translators, cleaning staff, etc.) were excluded from the study.

Data collection

An online survey was created in Turkish, Arabic, and English languages and distributed to HCWs working at RHCs via email, WhatsApp, or short message service. HCWs were asked to choose and fill out the survey form in the language they were most comfortable with. The survey consisted of 31 questions, including the five questions about HCWs' characteristics (occupation, region of employment, duration of employment, participation in breastfeeding counseling course) and 26 questions about HCWs' observations of Syrian mothers' breastfeeding and infant feeding practices. The survey included open-ended questions ($n=14$). The Arabic survey forms were translated from Turkish by bilingual Syrian translators and back-translated into Turkish for accuracy. The same process was applied by the researchers for the English survey forms. At the beginning of the survey, 10 forms in each language were filled by the health personnel, the incomprehensible questions were reviewed, and the study form was rearranged.

Qualitative data obtained through Arabic forms were translated by bilingual translators. All qualitative data were grouped appropriately. Care was taken to create a large number of groups in order to avoid data loss and to fully understand the subject. For the same purpose, the proportions of the answers forming the groups were given as a separate table.

Statistical analysis

The data were analyzed using the IBM-SPSS 23.0 program (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to check for normal distribution of data. Descriptive statistics were used to present continuous variables as mean±standard deviation and categorical variables as frequency and percentage. Chi-square test or Fisher's Exact test was used for comparisons between categorical variables. Subgrup analysis of proportions according to regions was performed using residual analysis with the Chi-square test. A significance level of $p<0.05$ was used.

Results

A total of 1161 survey forms were collected. Forms filled by HCWs of different nationalities or non-medical staff were excluded. In the end, 876 survey forms were suitable for analysis. However, 12 forms had been left blank in the question of the place of employment and the analyzes for working region were made in 864 survey forms.

The results of the study showed that out of the 876 Syrian HCWs included in the study, 37.3% were physicians and 62.7% were nurses or midwives. Most of the HCWs had been working for more than one year (45.4%). A small percentage (14.5%) preferred to fill out a Turkish survey form, and only 12% had attended a breastfeeding counseling course. The distribution of HCWs varied across different regions, with the highest proportion in the south (40.2%) and the lowest in the central region (9.4%) (Table 1).

HCWs' observations for breastfeeding characteristics of Syrian refugees were given in Table 1 and breastfeeding problems in Syrian refugees in Table 2. Regarding breastfeeding practices, 40% of HCWs reported that babies were fed only with breast milk in the first three days after birth. HCWs stated the highest use of prelacteal foods such as sugary water in the East region and the lowest usage in the West ($p<0.001$, Table 1). HCWs mentioned the highest frequency of herbal tea usage in the East ($p<0.05$). Reported prelacteal foods by HCWs are seen in Table 3.

HCWs stated "the initiation of breastfeeding within one hour" for most Syrian mothers (Table 1). They cited "Not feeling well physically or mentally after delivery" as the most common reason (8.6%) for not achieving the initiation of breastfeeding within one hour. Almost half of those was "maternal mental illness" (3.8%) (Table 4). The initiation of breastfeeding within one hour was reported less frequently in the East region and among physicians (Table 1). More than one-third HCWs remarked "Breast milk insufficiency or breastfeeding problems" as the first common reason for shorter breastfeeding duration (Table 1). One-fifth stated "Factors related to maternal health" as the second reason in which the rates of statement were changed according the working region and profession of HCWs; highest in Central Region and Physicians questionaries. The answer "Factors related to maternal health" included not only physical but also mental health (Table 4). "Lack of experience or education" and "Frequent pregnancy plan" were the other frequent reasons stated by HCWs (Table 4).

HCWs reported that exclusive breastfeeding duration was less than six months in more than half of Syian infants and total breastfeeding duration was less than six months in one-tenth (Table 1). The total breastfeeding duration less than six months was stated highest in the east region and the lowest in the central region (15.2%, 3.7%, respectively).

Overall, 28.0% of HCWs stated early introduction of complementary feeding and 7.4% remarked delayed starting for complementary feeding. Early introduction of complementary feeding was reported more by physicians, whereas delayed introduction for complementary feeding by nurses ($p<0.001$, $p<0.05$; respectively). About 27.4% of the HCWs said that they usually observed that more than half of the mothers gave formula in the first six months (Table 1).

HCWs believed grains, fruits and vegetables, and dairy products as top three foods for starting complementary food (59.5%, 47.8%, and 30.3% respectively). The belief of HCWs was changed with working region for grains and dairy products (Table 1). A small number of HCWs (0.9%) said that mothers usually gave unsuitable foods (tea bread mix, coffee and honey) for complementary feeding (Table 3).

A quarter of HCWs stated breastfeeding difficulties as a common problem (Table 2). More physicians than nurses stated breastfeeding difficulties as a common problem (31.6%, 23.4%, $p<0.01$). Overcoming more than half problems were reported in 70.7% of HCWs and this was similar in physicians and nurses. HCWs in the Central Region reported the lowest success rate for the management of the half of breastfeeding problems (55.6%).

"Lack of experience or education", " Maternal-related factors", "Lactation-related problems", and "Economic problems" were the top four difficulties (10.7%, 9.5%, 5.8%, and 5.4%, respectively) associated with breastfeeding according to HCWs utterance (Table 2). According to 69.1% of HCWs, grandmothers were identified as the primary source of support for lactating mothers. The majority of HCWs (68.6%) reported that breastfeeding was immediately stopped when the mother became pregnant, and only 29.6% of HCWs reported that tandem feeding was practiced (Table 2).

Healthcare challenges of Syrian pregnant and lactating mothers posed by HCWs were given in detail in Table 5. "Food-finance-housing-related problems" (34.9%), "low maternal education" (27.3%) and "cultural and environmental issues" (19.6%), maternal health-related problems (18.6%), and challenges for family planning (15.4%) were frequently observed problems related to healthcare and nutritional characteristics of pregnant women and mothers (Tables 2 and 5). Some observations were changed according to region; utterence for finance problems mostly reported in South region, low maternal education in South and Central region. In addition, Central region reported more cultural and environmental problems and problems with family planning (Table 2).

Details of recommendations of HCWs to solve the difficulties experienced by Syrian mothers were seen in

Table 1 HCWs' observations for breastfeeding characteristics of Syrian refugees

	Total	HCWs' Job, %[a]		Working Region, %[a]			
	%[a]	Physician	Nurse	West	South	Central	East
Overall, n	876	327	549	199	352	82	231
(%)[b]		(37.3)	(62.7)	(22.7)	(40.2)	(9.4)	(26.4)
Mothers, usually observed to give only breast milk to their babies in the first three days	40.0	**34.6**	**43.9***	**51.8**^{x}	**35.5**^{y}	**52.4**^{x}	**32.5**^{y***}
Prelacteal foods usually observed to be given							
Sugary water	45.2	50.5	42.1	**32.7**^{x}	**49.7**^{y,z}	**39.0**^{x,y}	**51.9**^{z***}
Dairy products	8.7	10.1	7.8	9.0	8.2	9.8	9.1
Herbal tea	3.2	3.1	3.3	**2.5**^{x,y}	**2.3**^{x}	**1.2**^{x,y}	**6.1**^{y*}
Pure water	3.0	1.8	3.6	2.0	3.1	2.4	3.9
Sweet food	2.5	2.8	2.4	3.5	2.0	6.1	1.3
Usually observed the initiation of breastfeeding within one hour							
Frequently	91.6	**86.5**	**94.7*****	**93.4**^{x}	**94.0**^{x}	**93.9**^{x}	**85.7**^{y**}
Reasons for not achieving the initiation of breastfeeding within one hour							
Not feeling well physically or mentally after delivery	8.6	**14.1**	**5.3*****	5.5	8.8	11.0	10.0
Lack of experience or education	5.3	7.0	4.2	3.5	4.5	8.5	6.9
The belief of there is not enough breast milk	3.3	3.7	4.0	3.5	3.1	1.2	6.5
Illness of the mother or baby	3.0	4.0	2.4	1.5	3.1	6.1	2.6
Usually observed exclusive breastfeeding duration							
≥6 months	49.2	**35.9**	**57.1*****	52.0	45.7	54.9	50.0
4–5 months	40.8	**52.8**	**33.7*****	37.4	44.3	34.1	40.4
First 3 months	10.0	11.3	9.2	10.6	10.0	11.0	9.6
Opinion for the reason why exclusive breastfeeding is shorter than six months							
Breast milk insufficiency or breastfeeding problems	37.2	40.4	35.3	34.2	37.2	56.1	33.3
Factors related to maternal health	20.7	**26.0**	**17.5****	**22.1**^{y}	**22.4**^{y}	**32.9**^{z}	**12.1**^{x***}
Lack of experience or education	10.3	16.8	6.4	10.6	10.2	12.2	9.5
Frequent pregnancy plan	10.0	8.0	11.3	**4.0**^{x}	**16.8**^{y}	**8.5**^{x,y}	**5.6**^{x***}
Mother's job-economic problems	4.7	**7.6**	**2.9****	**4.5**^{x}	**7.1**^{x}	**2.4**^{x,y}	**1.3**^{y**}
Culture-social environment	3.3	**93.9**	**98.4*****	4.5	2.0	6.1	2.6
Illness of children	3.2	2.1	3.8	2.0	5.1	3.7	1.3
Usually observed total breastfeeding duration							
<6 months	10.5	8.6	11.7	**9.6**^{x,y}	**9.1**^{x,y}	**3.7**^{x}	**15.2**^{y*}
<12 months	30.5	28.1	31.9	29.1	30.4	23.2	34.2
Usually observed infants receiving formula in the first six months							
More than half	27.4	25.3	28.6	32.7	24.3	21.0	29.1
Usually observed complementary feeding starting time							
<6 months	28.0	**38.2**	**21.9*****	30.7	30.7	26.8	22.1
≥9 months	7.4	**4.9**	**8.9***	8.5	7.4	7.3	6.9
Foods that are usually observed to be started first in complementary feeding							
Grains	59.5	61.5	58.3	**51.8**^{x}	**59.1**^{x,y}	**62.2**^{x,y}	**65.8**^{y*}
Fruits and vegetables	47.8	49.8	46.6	48.2	49.4	51.2	44.6
Dairy products	30.3	27.5	31.9	**23.6**^{x}	**33.0**^{y}	**40.2**^{y}	**29.0**^{x,y*}
Soups-snacks	9.0	7.0	10.2	6.5	7.4	12.2	12.1
Egg	4.6	3.4	5.3	5.0	4.8	4.9	3.9

[a]Column percentage; [b]Row percentage; Comparison according to HCWs' job and working region; *p<0.05, **p<0.01, ***p<0.001; The letters x,y,z indicate the statistically significant difference between the subgroups of the working region

Table 6. More than half of HCWs recommended "supporting breastfeeding" to solve the difficulties experienced by Syrian mothers (Tables 2 and 6). Nearly one-third recommended "nutrition and health support to the mother". More than one-tenth of HCWs recommended "family planning" to solve the difficulties. This recommendation was most expressed in the Central region (23.2%) and less stated in the East region (7.8%) ($p<0.01$; Table 2). Compared to nurses, more physicians recommended "Regulating the health system legislation" ($p<0.05$).

HCWs identified various healthcare challenges faced by Syrian pregnant and lactating mothers, including food, finance, and housing-related problems, low maternal

Table 2 HCWs' observations for breastfeeding problems in Syrian refugees

	Total	HCWs' Job, %[a]		Working Region, %[a]			
	%[a]	Physician	Nurse	West	South	Central	East
Overall, n	876	327	549	199	352	82	231
(%)[b]		(37.3)	(62.7)	(22.7)	(40.2)	(9.4)	(26.4)
Are breastfeeding difficulties common according to HCWs observations?							
Yes	26.5	**31.6**	**23.4****	24.4	24.1	28.0	29.0
Rate of overcoming breastfeeding difficulties according to HCWs observations							
More than half	70.7	70.6	70.7	**71.8**^{x}	**73.9**^{x}	**55.6**^{y}	**71.9**^{x*}
Most common observed difficulties associated with breastfeeding according to HCWs observations							
Lack of experience or education	10.7	12.2	9.8	9.0	9.4	13.4	13.0
Maternal-related factors	9.5	9.8	9.3	10.6	8.2	12.2	9.1
Lactation-related problems	5.8	7.6	4.7	6.0	4.3	6.1	7.8
Economic problems	5.4	7.6	4.0	5.5	6.8	3.7	3.0
Culture-related problems	3.2	4.3	2.6	3.0	2.8	6.1	2.6
Factors related to family planning	3.0	4.0	2.4	**1.5**^{x}	**3.7**^{x,y}	**7.3**^{y}	**1.7**^{x*}
From whom do lactating mothers usually get support in baby feeding according to HCWs observations?							
Mothers of her or her husband	69.1	69.9	68.9	68.3	71.3	74.4	64.9
Health care professionals	32.3	30.9	33.2	30.7	34.4	32.9	32.0
Other people	17.0	78.3	85.8	21.1	15.3	23.2	13.9
Husbands	9.7	89.0	91.1	13.1	8.0	13.4	8.7
When getting pregnant again while breastfeeding							
Usually breastfeeding is stopped	68.6	**60.0**	**73.8*****	69.5	70.4	57.3	70.5
How long does breastfeeding usually continue while pregnant according to HCWs observations?							
Discontinued immediately or in the first trimester	71.9	69.1	73.6	69.8	74.4	64.6	73.2
Discontinued in the 2nd trimester	11.4	11.3	11.5	9.0	11.6	18.3	11.3
Discontinued in the 3rd trimester	2.3	2.4	2.2	2.0	2.6	1.2	2.2
Depending on the age of the breastfed child	6.7	8.3	5.8	7.5	5.7	8.5	6.1
Other	6.7	1.5	0.9	2.0	0.9	2.4	0.4
Missing	6.5	7.3	6.0	9.5	4.8	4.9	6.9
Is tandem breastfeeding common according to HCWs observations?							
Yes	29.6	32.0	28.2	29.7	28.7	24.7	33.0
Healthcare challenges of Syrian pregnant and lactating mothers posed by HCWs							
Food-finance-housing-related problems	34.9	36.4	34.1	**28.1**^{x}	**42.9**^{y}	**32.5**^{x,y}	**29.0**^{x**}
Low maternal education	27.3	29.7	25.9	**25.1**^{x,y}	**31.0**^{y}	**31.7**^{y}	**21.2**^{x*}
Cultural and environmental issues	19.6	19.6	19.7	**14.6**^{x}	**20.5**^{x,y}	**29.3**^{y}	**19.0**^{x,y*}
Maternal health-related problems	18.6	18.0	18.9	16.1	20.5	14.6	18.6
Problems with family planning	15.4	16.2	14.9	**10.1**^{x}	**15.1**^{x}	**30.5**^{y}	**15.6**^{x***}
Incorrect nutrition practices	8.9	9.5	8.5	8.0	9.1	8.9	9.6
Breastfeeding-related problems	5.5	5.5	5.5	5.0	6.0	1.2	6.9
Lack of health care	4.8	4.9	4.7	3.5	6.8	6.1	2.6
Recommendations of HCWs to solve the difficulties experienced by Syrian mothers							
Supporting breastfeeding	57.2	58.4	56.5	50.8	59.4	57.3	59.7
Nutrition, health support to the mother	35.7	67.6	62.3	28.1	39.5	34.1	36.8
Family planning	12.7	13.8	12.0	**11.1**^{x,y}	**14.8**^{y,z}	**23.2**^{z}	**7.8**^{x**}
Regulating the health system-legislation	8.6	**11.6**	**6.7***	8.0	6.5	11.0	10.8

[a]Column percentage; [b]row percentage; Comparison according to HCWs' job and working region: *p<0.05, **p<0.01, ***p<0.001; The letters x,y,z indicate the statistically significant difference between the subgroups of the working region.

education, cultural and environmental issues, and challenges related to family planning (Table 5). Recommendations to address these difficulties included supporting breastfeeding, providing nutrition and health support to mothers, and promoting family planning (Table 6). Trained HCWs who had attended a breastfeeding counseling course had different perspectives compared to their counterparts in some areas, such as the role of culture and social environment, maternal-related factors, and paternal support.

Table 3 Prelacteal feeding and complementary feeding characteristics of Syrian refugees according to HCWs' observation

What foods are given to the baby in the first three days after birth, other than breast milk according to HCWs' observation?	n (%)	With which foods do mothers start complementary feeding, according to HCWs' observation?	n (%)
Sugary water	396 (45.2)	Grains	521 (59.5)
Dairy products	76 (8.7)	• Rice or rice flour	350 (40.0)
• Milk	57 (6.5)	• Wheat flour or wheat starch	116 (13.2)
• Formula	16 (1.8)	• Baby food with grain	89 (10.2)
• Marjujah (goat milk with tea)	2 (0.2)	• Biscuit	12 (1.4)
• Yogurt	1 (0.1)	• Bread	4 (0.5)
Herbal tea	28 (3.2)	• Oat	2 (0.2)
• Anise tea	24 (2.7)	Fruits and vegetables	419 (47.8)
• Cumin tea	4 (0.5)	• Fruit puree or boiled fruit	280 (32.0)
• Mint tea	2 (0.2)	• Boiled vegetables	177 (20.2)
• Herbal tea	2 (0.2)	• Banana	51 (5.8)
Plain water	26 (3.0)	• Fruit juice	50 (5.7)
• Plain water	25 (2.9)	• Tomato juice	6 (0.7)
• Zamzam (sacred water)	1 (0.1)	• Avocado	1 (0.1)
Sweet food	22 (2.5)	Dairy products	265 (30.3)
• Date	9 (1.0)	• Milk	172 (19.6)
• Fruit	6 (0.7)	• Yoghurt	105 (12.0)
• Honey	3 (0.3)	Soups-snacks	79 (9.0)
• Turkish delight	2 (0.2)	• Soups	72 (8.2)
• Grape molasses	1 (0.1)	• Snacs	7 (0.8)
		Egg	40 (4.6)
		Flesh foods	5 (0.5)
		• Red meat	3 (0.3)
		• White meat	2 (0.2)
		Unsuitable foods	8 (0.9)
		• Tea bread mix	3 (0.3)
		• Coffee	3 (0.3)
		• Honey	2 (0.2)

Discussion

According to the observations of HCWs, Syrian mothers usually start breastfeeding within the first hour, breastfeed their babies exclusively for the first six months, and stop breastfeeding after 12 months in our study. However, more than half of HCWs said mothers usually give prelacteal foods and nearly one-third said mothers start complementary foods before six months. According to the TDHS 2018 Syrian sample, 73% of children started breastfeeding within the first hour, 24% received prelacteal foods, and the frequency of exclusive breastfeeding was 6% for infants aged 6–8 months [10]. Previously, a study conducted in Turkey revealed that the rate of exclusive breastfeeding≥6 months in Syrian babies was 28.1%, the rate of the initiation of breastfeeding within one hour was 61.4%, and all the breastfeeding indicators in Syrian refugees were lower than that for local women in Turkey [5]. In a study conducted in Lebanon, the percentages of prelacteal feeding, the initiation of breastfeeding within one hour, and the exclusive breastfeeding were 62.5%, 31%, and 24.6% respectively, in Syrian refugees [11]. It was seen that HCWs in this study perceived breastfeeding rates higher than they were in previous surveys. As shown, the breastfeeding attitudes of Syrian refugees vary according to the country and region where the study is conducted. There are also regional differences in this study.

Most of the HCWs said prelacteal feeding was common among Syrian refugees. As a prelacteal food, the HCWs observed sugary water usage more common in the south and east regions closer to the Syrian border than in the western region far from the border. In addition, milk, formula, and herbal teas were stated as prelacteal food. In a study conducted in Jordan, it was found that 64.3% of Syrian refugee mothers gave prelacteal foods to their babies; of them, water (99.7%), sugary water (64.5%), milk-formula (52.7%), and herbal tea (29.3%) were most frequently given [12]. In a qualitative study conducted in Turkey, most Syrian mothers said they gave prelacteal foods such as sugary water, packaged fruit juice, infant formula, anise, dates, honey, cumin, and Zamzam (religiously blessed plain water) [6].

HCWs identified maternal health conditions, including malnutrition, as the primary barriers to initiating

Table 4 Breastfeeding barriers according to HCWs' observations

What is the reason why babies cannot be breastfed within the first hour after birth?	N (%)	The reason why exclusive breastfeeding is shorter than six months	N (%)
Not feeling well physically or mentally after delivery	75 (8.6)	**Breast milk insufficiency or breastfeeding problems**	326 (37.2)
• Mother's postpartum fatigue and pain	42 (4.8)	• Insufficient breast milk production	244 (27.9)
• Mother's mental illness	33 (3.8)	• Insufficient weight gain of the child	34 (3.9)
• Nipple pain	2 (0.2)	• Frequent crying / not getting enough of the baby	33 (3.8)
Lack of experience or education	46 (5.3)	• Believing that breast milk is not enough	32 (3.7)
• Mothers do not know how to breastfeed and are inexperienced	41 (4.7)	• Breast problems	16 (1.8)
• Unable to attach baby to breast	6 (0.7)	• Breast rejection	7 (0.8)
The belief of there is not enough breast milk	29 (3.3)	• Artificial feeding	5 (0.6)
• Failure of milk to reach the breast	32 (3.7)	• Twin birth	4 (0.5)
• Baby's crying or not getting enough	1 (0.1)	**Factors related to maternal health**	181(20.7)
Illness of the mother or baby	26 (3.0)	• Maternal poor health/drug use	107 (12.2)
Delivery type	19 (2.2)	• Maternal malnutrition	79 (9.0)
• Cesarean delivery	16 (1.8)	• Mother's mental illness	15 (1.7)
• General anesthesia given during delivery*	6 (0.7)	• Aesthetic concerns	5 (0.6)
Cultural misconception	13 (1.5)	• Desire to gain weight	3 (0.3)
Deficiencies in Baby-Friendly Hospital Initiative implementation	3 (0.3)	• Absence of mother	2 (0.2)
• Uneducated health professionals	1 (0.1)	**Lack of experience or education**	90 (10.3)
• The impact of formula companies in the hospital	1 (0.1)	• Not knowing the importance of breast milk, no education	77 (8.8)
• Doctors recommend formula	1 (0.1)	• Mother's inexperience	13 (1.5)
		• Lack of health care	6 (0.7)
		Frequent pregnancy plan	88 (10)
		Mother's working conditions-economic problems	41 (4.7)
		• Mother's work	27 (3.1)
		• Economic problems	15 (1.7)
		Culture-social environment	29 (3.3)
		Illness of children	28 (3.2)

*The belief that breastfeeding should not be done immediately after cesarean section because the mother has taken medication

breastfeeding within one hour and exclusive breastfeeding. Half of the HCWs believed that supporting mothers, and one out of every three said that providing them with nutritional and health support would help address breastfeeding problems. The study also highlighted the impact of social determinants of health, such as food insecurity, maternal physical and mental health, family income, housing, education, working conditions, and the sociocultural environment, on breastfeeding attitudes and practices. According to a qualitative study conducted in Turkey, Syrian refugees think that breastfeeding negatively affects maternal health and that lactating mothers should be well-fed [6]. In a mixed-method study conducted with Syrian refugees in Lebanon, maternal health was defined as one of the barriers to breastfeeding [11]. In a qualitative study conducted in eastern Uganda, women highlighted hunger as a cause of insufficient milk production [13]. A study conducted in South Africa found that mothers living in low socioeconomic conditions and experiencing hunger breastfeed less frequently [14]. According to a study conducted in Kenya, it was predicted that women living in houses with no food security would not be able to breastfeed their babies exclusively in the first six months, women who gave only breast milk for six months would experience health or social problems, and women would need sufficient food to support breastfeeding [15]. The maternal experience of hunger can contribute to perceived milk insufficiency, anxiety about infant hunger, and a perception that access to adequate food is necessary for successful breastfeeding [13–15]. Therefore, breastfeeding support should include nutritional and economic support for the mother. In addition, household food insecurity was among the situations that limited breastfeeding in many studies [16–20].

Maternal mental health is reported as a barrier to breastfeeding in our study. Some studies reported that postpartum depression and anxiety were associated with the discontinuation of breastfeeding, especially in refugees [6, 21, 22]. In a recent systemic review, 12 of 33 studies reported significant positive effects of behavioral interventions on maternal mental health and breastfeeding success [23]. On the other hand, a previous study

Table 5 Healthcare challenges of Syrian pregnant and lactating mothers posed by HCWs according to HCWs' observations

Challenges	N(%)
Food-finance-housing-related problems	**306 (34.9)**
• Malnutrition of the mother or child	200 (22.8)
• Financial deficiencies/poor living conditions	115 (13.1)
• Mother's work	34 (3.4)
• Expensive, paid/not-free formulas	4 (0.5)
Low maternal education	**239 (27.3)**
Cultural and environmental issues	**172 (19.6)**
• Ignoring recommendations/not attending following up	113 (12.9)
• Cultural barriers	73 (8.3)
• Adolescent marriage/adolescent pregnancy	61 (7.9)
• Tetanus vaccine refuse (in pregnancy)	6 (0.7)
• Divorces/marriage problems	5 (0.6)
• Unsafe abortions	1 (0.1)
Maternal health-related problems	**163 (18.6)**
• Maternal poor health/drug use	56 (6.4)
• Psychological problems	50 (5.7)
• Maternal anemia	40 (4.6)
• Poor hygiene of mother and baby	25 (2.9)
• Not wanting to breastfeed	8 (0.9)
• Aesthetic concerns	2 (0.2)
• Not drinking a lot of water	1 (0.1)
Challenges for family planning	**135 (15.4)**
• Short pregnancy interval/getting pregnant while breastfeeding	124 (14.2)
• Absence or refusal of family planning	11 (1.3)
• Leaving breastfeeding to get pregnant again	2 (0.2)
Incorrect mothers' nutrition practices	**78 (8.9)**
• Starting complementary feeding early	19 (2.2)
• Unnecessary/inappropriate formula feeding	18 (2.1)
• Negligence of baby	12 (1.4)
• Concerns about breast milk's sufficient and baby growth	11 (1.3)
• Breastfeeding while pregnant	8 (0.9)
• Early weaning	8 (0.9)
• Not breastfeeding immediately after birth	4 (0.4)
• Feeding baby with cow milk	3 (0.3)
• Pacifier use	3 (0.3)
• Starting complementary feeding late	2 (0.2)
• Trying to lose weight while breastfeeding	2 (0.2)
• Not breastfeeding while pregnant	1 (0.1)
• Late weaning	1 (0.1)
• Cessation breastfeeding due to jaundice	1 (0.1)
Breastfeeding-related difficulties	**48 (5.5)**
• Breast problems	37 (4.2)
• Insufficient breast milk	14 (1.6)
Lack of health care	**42 (4.8)**
• Insufficient pregnant-baby follow-up/difficulty of reaching health centers	39 (4.5)
• Mothers who do not have IDs do not apply to health centers.	3 (0.3)

Table 6 Recommendations of HCWs to solve the difficulties experienced by Syrian mothers according to HCWs' observations

Recommendations	N (%)
Supporting breastfeeding	**501 (57.2)**
• Educating breastfeeding mothers	457 (52.2)
• Solving breast problems	34 (3.9)
• Initiating breastfeeding immediately after birth	21 (2.4)
• Frequent breastfeeding	20 (2.3)
• Cleaning or wiping the breast	20 (2.3)
• Providing formula to mothers who cannot breastfeed	1 (0.1)
Nutrition and health support to the mother	**313 (35.7)**
• Feeding mothers well, ensuring adequate nutrition of the mother	241 (27.5)
• Psychological support for mothers	54 (6.2)
• Vitamin supplement for mother	53 (6.1)
• Increasing family income / providing food aid	40 (4.6)
• Encouraging mothers to breastfeed	25 (2.9)
• Mothers should pay attention to cleanliness	20 (2.3)
• Arrangement of working hours of mothers	7 (0.8)
• Reducing odors and deodorants	1 (0.1)
Family planning	**111 (12.7)**
Regulating the health system-legislation	**75 (8.6)**
• Periodic follow-up of mothers and babies	49 (5.6)
• Educating healthcare personnel	12 (1.4)
• Formula sales must be by prescription or warnings should be written on the boxes	8 (0.9)
• To open comprehensive and widespread health centers	3 (0.3)
• Information through the media	2 (0.2)
• Researching on problems	2 (0.2)
• Providing convenience to nurses	1 (0.1)
• Providing breastfeeding rooms	1 (0.1)
Overcoming cultural barriers	**15 (1.7)**
• Prevention of adolescent marriages	10 (1.1)
• Overcoming language and culture barriers	5 (0.6)

showed a significant relationship between maternal symptoms of mental health problems and breastfeeding self-efficacy [24], showing the importance of multidimensional interaction [6, 25].

Overall, HCWs have associated the mother's breastfeeding status with factors such as the mother's physical and mental health, family income, housing, education, working conditions, inability to access quality health care, and socio-cultural environment. All these factors are also social determinants of health [26]. As a result of studies conducted in the United States, education, employment, food, neighborhood, housing, family income, and discrimination have been defined as social determinants of breastfeeding, and interventions targeting these determinants have been proposed to improve breastfeeding rates [27].

The Baby Friendly Hospital Initiative is the principal program to support breastfeeding and is based on the Ten Steps [28]. Nine of these steps involve hospital practices, while step 10 (Community Support) is about

maintaining breastfeeding support after discharge from the maternity hospital. Step 10 appears to be key for the long-term sustainability of the short-term breastfeeding gains obtained due to the Baby Friendly Hospital Initiative efforts focusing solely on maternity facilities. Facilities providing maternity and newborn services need to identify appropriate community resources for continued and consistent breastfeeding support that is culturally and socially sensitive to their needs. These include guidance in primary healthcare centers, mother-to-mother support, family support, and advertisement of breastfeeding [6, 29–32]. Therefore, extending step 10 to target the social determinants of breastfeeding should be considered. In Turkey, primary health care is provided to refugees in RHCs. Only 12% of the HCWs in these centers received breastfeeding counseling training during the study period. With the results of this study, breastfeeding counseling training for HCWs was initiated in RHCs.

The study acknowledged some limitations. The study was conducted in RHCs in Turkey, and the selection of Syrian HCWs was not randomized, and may not be generalizable to other settings or populations. The study relied on personal observations of HCWs and provided only second-hand information. Also, most of the HCWs did not have breastfeeding counseling courses, and the adequacy of trained HCWs was controversial. Some HCWs may be woefully ignorant about infant feeding, subject to recall or social desirability bias. As a limitation of the self-administered survey, since these statements were not followed up and controlled in the study design, it is unknown whether the health professionals solve these problems, which problems, and to what extent they solve them. This study was not conducted directly with mothers and focused on the perspectives of HCWs, limiting a comprehensive understanding of mothers' experiences and attitudes toward breastfeeding. But the fact that the included HCWs were from the same community. The study was conducted within a specific timeframe and may not capture the long-term trends or changes in breastfeeding practices among Syrian refugee mothers. Despite these limitations, the study emphasized the need for supporting breastfeeding among vulnerable populations like refugees. This study can be both a stepping stone to future qualitative studies and a guide to interventions that target the social determinants of breastfeeding in refugees.

Conclusions

According to HCWs observations, prelacteal feeding and giving sugary water within 2–3 days after birth are quite common among Syrian refugees, and the most important barriers to breastfeeding are thought to be the lack of education, poor mental and physical health of the mother, food insecurity, low income, housing, lack of family planning, sociocultural environment and the inability to access quality health services. In order to increase breastfeeding rates in refugees, intervention programs including the social determinants of breastfeeding should be developed and integrated into Step 10 of the Baby Friendly Hospital Initiative, especially food aid to breastfeeding mothers, training of primary healthcare workers, and increasing the quality of care.

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Authors' contributions
SSY: Designed the study and the analytical strategy and helped to interpret the findings, critically reviewed the manuscript; MEN: Designed the study, interpreted the findings, conducted the literature review, wrote the manuscript and revised the manuscript after critical review; SY: Designed the analytical strategy, interpreted the findings, critically reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability
The data of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests
The authors declare no competing interests.

Ethics
Hacettepe University, Non-Interventional Clinical Research Ethics Committee and Ministry of Health approved the original surveys. This study was performed in line with the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

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