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Musculoskeletal and Rheumatic Diseases as Emerging Risk Factors for Reduced Fertility

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ABSTRACT.

The importance of musculoskeletal diseases (MSDs) and related immune mediated rheumatic conditions in both women and men is becoming more widely recognized, but underappreciated, as significant contributors to decreased fertility and adverse pregnancy outcomes. During assisted reproductive technology (ART) cycles, there is evidence accumulating from population-based registries, systematic reviews, and clinical cohort studies that indicate that individuals with various conditions like rheumatoid arthritis, systemic sclerosis, juvenile idiopathic arthritis, and others experience elevated rates of subfertility, childlessness, miscarriage, and complications. The biological mechanisms that directly affect gamete quality, implantation, and placental function include hormonal dysregulation, oxidative stress, chronic systemic inflammation, and direct effects. Significant knowledge gaps persist, particularly regarding male fertility and specific nonautoimmune MSDs, despite recent clinical guidelines advocating integrated reproductive health care for these patients. To address this overlooked aspect of health promotion, this editorial calls for a greater level of clinical awareness, regular preconception counseling, multidisciplinary collaboration between rheumatologists, orthopaedists, and reproductive specialists, and dedicated research funding.

Keywords: musculoskeletal diseases; rheumatic diseases; infertility; pregnancy outcomes; assisted reproductive technology; reproductive health; inflammation.

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Introduction

For many years, patients with rheumatic and musculo-skeletal diseases have received much more attention for their joint pain, functional limitations, or systemic inflammations than for their reproductive health. However, increasing amounts of high quality research now show that these conditions many of which peak in the prime of reproduction are consistently associated with lower fertility, more pregnancies aborted and poorer outcomes after ART. This editorial summarises recent epidemiological, mechanistic and clinical findings to argue that the link between MSD and fertility should be a key component of integrated patient care and health promotion (Boussaid et al., 2022).

There is no longer any doubt about the connection between musculoskeletal conditions and abnormal reproduction. Skomsvoll et al. conducted a population-based study of women between the ages of 40 and 42. (2000) discovered that compared to women without MSDs, those with chronic musculoskeletal disorders had a much higher percentage of subfertility and longer intervals between pregnancies (Skomsvoll et al., 2000). More recently, a nationwide Finnish registry study encompassing 19 immune-mediated diseases (Kerola et

al., 2024) demonstrated increased childlessness and fewer children among patients with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), and several other inflammatory rheumatic diseases. Notably, similar patterns were observed in men, a group historically overlooked in fertility research. Chandrashekara et al. in systemic sclerosis. (2025) confirmed reduced fertility and increased rates of miscarriage, including higher rates of miscarriage and (Chandrashekara et al., 2024).

In this population, pregnancy complications also tend to cluster. Kerola and associates. (2024) found that women with inflammatory rheumatic diseases are more likely to experience pre-eclampsia, preterm delivery, small-for-gestational-age infants, non-elective cesarean sections, and admission to the neonatal intensive care unit; SLE and Sjögren's syndrome have the most severe effects (Kerola et al., 2024). Wider reproductive disorders such as endometriosis, adenomyosis, fibroids and polycystic ovarian syndrome, which share inflammatory and hormonal pathways with MSD, also increase the risk of preterm birth, foetal growth suppression and placental pathologies (Vannuccini et al., 2015).

The prognosis for patients with rheumatic or musculo-skeletal disorders undergoing ART appears to be less favourable than for the general population. Systematic review and meta-analysis by Kontogiannis (2026) found that immune-mediated rheumatic diseases, in particular Sjögren's syndrome and rheumatoid arthritis, are associated with a decrease in live births per embryo transfer and overall in live births across disease categories (Kontogiannis et al., 2026). In a single-centre ART cohort, Manouchehri et al. (2025) confirmed higher miscarriage risks and more frequent inadequate gestational weight gain among women with rheumatic diseases compared to controls(Manouchehri et al., 2026).

Similar patterns are seen in other long-term immune-mediated disorders. Although IVF pregnancy rates in non-operated ulcerative colitis may be similar to those in non-IBD populations, inflammatory bowel disease, especially Crohn's disease, is associated with decreased fertility when the disease is active (Vieujean et al., 2022). Large registry data in multiple sclerosis indicate that, after adjusting for confounders, there is no discernible difference in live birth or clinical pregnancy following ART; however, relapse risk may rise in the vicinity of ART procedures (Sparaco et al., 2023).

Disproportionately little research has been done on how rheumatic and musculoskeletal conditions affect male fertility. Boussaid et al. conducted a systematic review. (2022) found that men with autoimmune rheumatic diseases had higher rates of varicocele, hormonal abnormalities, and poorer semen quality (Boussaid et al., 2022). Moreover, it is evident that some medications that modify disease, such as cyclophosphamide, are gonadotoxic. Kerola and associates. (2024) found that men with inflammatory rheumatic diseases also have lower fertility and more childlessness, with impaired spermatogenesis and sexual dysfunction as potential causes (Kerola et al., 2024). In multiple sclerosis, population-based data suggest an association between MS and male infertility or fewer offspring, though altered sexual behaviour may contribute (Toljan & Briggs, 2024).

The main mechanistic theory for how rheumatic and musculoskeletal disorders affect fertility is chronic low-grade systemic inflammation, which interferes with the hypothalamic-pituitary-ovarian (HPO) axis, hinders

follicular development, and lowers oocyte quality. The endometrial environment can be directly harmed by pro-inflammatory cytokines, which can lower implantation receptivity and increase early pregnancy loss. MSDs and reproductive disorders share hormonal and inflammatory pathways (Vannuccini et al., 2015) offer a unifying framework: diseases like endometriosis and RA share prostaglandin dysregulation, interleukin-1, and tumor necrosis factor-α, all of which impact ovulation, fertilization, and placentation. Gamete DNA and mitochondrial function are further harmed in both sexes by oxidative stress, a feature of many MSDs.

Understanding the connection between MSD and infertility has immediate practical implications. Reproductive health is now specifically integrated into rheumatic and musculoskeletal care according to major guidelines. The American College of Rheumatology's 2020 Guidelines for Managing Reproductive Health in Musculoskeletal and Rheumatic Conditions emphasises contraception, preconception counselling, ART, fertility preservation, and multidisciplinary collaboration (Sammaritano et al., 2020). However, the same guideline highlights significant knowledge gaps and low levels of evidence, particularly for men and non-autoimmune MSDs (fibromyalgia, osteoarthritis, and chronic low back pain). Reproductive endocrinologists are rarely consulted by specialists in clinical practice, and many patients are never questioned about their reproductive plans.

For this reason, we recommend three concrete actions. First, all men and women of reproductive age who have been diagnosed with a serious MSD or rheumatic disease should receive regular fertility testing and preconception counseling. Second, it is necessary to create and assess integrated care pathways that connect rheumatology, orthopedics, obstetrics, and reproductive medicine. Third, specific funding for research is desperately needed to close the evidence gaps, especially for intervention trials that look at how disease control affects ART success and prospective cohort studies that quantify fertility risks across the whole spectrum of MSDs.

Conclusion

The evidence is now clear: musculo-skeletal and rheumatic diseases are not neutral in terms of fertility. They reduce the chances of conception, increase the risk of miscarriage and compromise the results of ART. These conditions pose an underestimated burden on reproductive health for both men and women. Health promotion in this context means moving beyond symptom-based treatment and embracing a holistic approach that includes family planning, fertility maintenance and coordinated multidisciplinary care. As acknowledged in the ACR 2020 Guidelines, knowledge gaps remain large--but the first and most important step is recognizing this as a problem. This editorial is a call to action for clinicians, researchers and policy makers to put reproductive health at the heart of their care for the musculoskeletal system.

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Independence Mechanisms in Health Education/Promotion and Public Health Departments: A Narrative Review

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ABSTRACT. As administrators try to restructure in the name of efficiency, the organizational structure of public-health schools is increasingly challenged. A recurrent question is whether Public Health (PH) and Health Education and Health Promotion (HEandHP) should remain distinct academic disciplines or be merged or absorbed into more public health fields. Drawing on philosophical foundations, professional associations, competence frameworks, staff requirements and documented organizational results, this narrative review summarizes the global evidence for (a) the independence of HE and PH as separate units, (b) the independence of PH as a separate unit and (c) the structural separation of the two units. The five areas in which we have reviewed the evidence are the WHO Essential Public Health Functions (EPHF), professional associations and certification, competence frameworks, philosophical bases and documented risks of departmental mergers. Peer reviewed publications from 2010 to 2026 as well as official reports from the WHO, CEPH, ASPHER, SOPHE, IUHP and NCHEC were also sources of information. The organizational structure of the Iranian schools of public health is discussed qualitatively as an illustrative national context. Instead of relying on a specific, independently verified institutional data set, this debate is based on the general prevalence of classic departments reported in the Iranian literature on higher education in the field of medicine. There were five converging findings. First, HE, HV, and PH are based on different philosophical traditions. Secondly, the various branches maintain separate professional associations and certificates. Thirdly, each is based on a different competence framework (the 22 CEPOL core competences versus the eight NCHEC core competences). Fourth, the WHO's 12 European PHD Units need a diverse and specialized staff, which is best trained in the different departments. Fifth, there are significant risks associated with documented departmental mergers and proposals for restructuring. These risks include loss of professional identity, weakened specialized competencies and resistance from stakeholders, which sometimes delayed or partly modified proposed mergers, but did not always reverse them. The five traditional departments, including HE and HE, remain the dominant organizational model in the Iranian medical science university system, while new areas (e.g. G. Health policy and health information technology are still relatively under-represented in the official department structures. The evidence is in favour of keeping the PH and HE&HP separate. The merging of these departments could compromise the capacity of the workforce, professional identity and the development of specialized skills. Instead of structural mergers, cross-disciplinary cooperation should be pursued through research centres, joint programmers and networks of expertise.

Keywords: health education; health promotion; public health; academic departments; professional identity; competency-based education; essential public health functions; organizational structure

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1. Introduction

1.1 The global context of departmental structure

The organisational structure of the public health schools has an impact on labour force development, research capacity and educational quality. The debate on separation of departments

is growing as organisations around the world are under pressure to maximise resources and increase administrative efficiency.

There is a recurrent question whether public health education and promotion (HEHP) should remain separate academic disciplines, merge or be integrated into more general public health disciplines. This issue has implications that go far beyond administrative facilitation: departmental structures influence careers, research priorities, student identity, faculty recruitment, and curricula. The decision to maintain or remove these restrictions therefore has a direct impact on the training of future health professionals and ultimately on the health of the population as a whole.

1.2 The specific challenge

This article discusses a three-level challenge: tier 1: the need for HE&HP to continue as an independent service. The HE&HP is a unique body of knowledge, methodology and expertise, which cannot be reduced to epidemiology, biostatistics or the management of health services. Its focus on programming, empowerment of communities and behavioural modification requires specialised training, which can best be provided by a dedicated academic unit. Tier 2: Reasons why PH should remain a separate unit. Public health has a unique professional identity, competency profile and career development profile due to its focus on disease prevention, population surveillance and systemic intervention. It is not a sub-speciality in any other area, including clinical medicine. Tier 3: The reasons why these two divisions should not be combined. Despite their complementary roles, HE&HP and PH are philosophically, professionally and functionally distinct. Combining them would blur these distinctions and reduce the capacity of each area to contribute meaningfully to public health.

1.3 Research gap and questions

Despite the high stakes involved in departmental structure, systematic evidence synthesis on the best organisation of HE, HPA and PH is still lacking and policy decisions are often motivated by administrative convenience rather than empirical data. To fill this gap, the review asks the following questions: - what philosophical and conceptual bases distinguish HE&HP from PH and other public health disciplines, as well as what are the documented risks and results of a merger or attempts at a merger? - what are the professional organisations, certification and competence frameworks for each area?

2. Methods

2.1 Study design and data sources

To address a policy issue that spans several policy areas, this review used a narrative evidence review structure with elements of a rapid evidence-based assessment. This method is suitable for the synthesis of heterogeneous evidence (peer reviewed studies, official reports, competence frameworks and institutional case studies). This work is presented in accordance with the established guidelines for narrative reviews, including SANRA criteria, as narrative reviews are not systematic reviews.

Evidence comes from official reports from WHO, CEPHR, ASPHER, SOPHE, IUHP and NCHEC; documented institutional case studies on departmental reorganisation; and peer reviewed literature indexed in PubMed and Google Scholar (2010-26). The search terms are all combined as follows: health education, health promotion, health policy, health policy, health services, department, merger, restructuring, and professional identity. Priority was given to literature published between 2020 and 2026, while important older studies were kept where they were relevant.

Note on national context data. *An earlier draft of this review quoted a specific data set (MOHME, 2025) which reported the exact percentages of the different faculties for 45 Iranian medical schools. Upon verification, this data set could not be traced to any available and cited source and was deleted. Instead, section 3.6 and section 4.5 below describe a general and qualitatively documented structure of the departments in Iranian medical schools, without the use of fictitious statistics. Readers seeking quantitative confirmation in the Iranian context should consider this an open empirical question for further exploratory research (section 4.6).*

2.2 Inclusion criteria and analysis framework

Sources were consulted which discussed the philosophical basis for these areas, the professional associations or certification specific to each area, the staff requirements or EHFF requirements, the documented results of departmental mergers or interdisciplinary cooperation models without structural mergers. The evidence analysis used five pillars: (1) philosophical and conceptual foundations; (2) professional organisations and certification; (3) competence and staff requirements; (4) EHFF requirements; and (5) documented organisational results and risks. Figure 1 summarises the whole process of collecting and synthesising evidence.



Figure 1. summarises the whole process of collecting and synthesising evidence

Note. *This diagram represents the qualitative evidence-gathering and synthesis process described in Section 2 (Methods). Consistent with the narrative-review design and the limitations disclosed in Section 4.6, no formal risk-of-bias tool, PRISMA-style record count, or grey-literature critical-appraisal instrument was applied quantitatively; source selection was purposive and thematic rather than exhaustive or systematically counted.*

3. Results

3.1 Philosophical and conceptual foundations: three distinct disciplines

The philosophical underpinnings of public health, health promotion and health education highlight the differences that justify their separation as distinct academic disciplines. Modernist tradition of health education. Health education, rooted in modernist traditions, places great emphasis on changing individual behaviour through the development of skills and the transfer of knowledge. The commitment to methodical, evidence-based design of interventions and quantifiable results is reflected in frameworks such as the PRECEDE-PROCEED (Green and Kreuter, 2005).

Post-modernist tradition of health advocacy. Health promotion, on the other hand, is based on a post-modernist and critical tradition that favours community participation, structural change, and empowerment. The Ottawa Charter (1986) called for action to tackle social determinants outside the health sector, framing health as an integral part of daily life (Laverack, 2007; Tones, 2003). Public health (population-based tradition). PH is rooted in a population-based tradition which favours systemic intervention, disease prevention and surveillance (Ashton .,2022) warned that important population health disciplines are marginalised when public health is confined to a biomedical or clinical context.

Key findings: These differences are not only academic; they shape curricula, research priorities and professional practice and are best maintained by a separation of departments (Table 1).

Table 1. Philosophical Foundations of Health Education, Health Promotion, and Public Health

Dimension	Health Education	Health Promotion	Public Health
Intellectual tradition	Modernist (behavioral science, educational theory)	Post-modernist (critical theory, empowerment)	Population-based (epidemiology, biostatistics)
Primary focus	Individual knowledge, attitudes, behaviors	Social determinants, structural change, empowerment	Population surveillance, disease prevention, health protection
Key concepts	Behavior change, health literacy, program planning	Empowerment, participation, social justice, policy	Surveillance, epidemiology, prevention, systems
Professional credential	CHES, MCHES	IUHPE registration	CPH

Note. Sources: Tones (2003); Laverack (2007); Green & Kreuter (2005).

3.2 Independent professional organizations and certifications

Further evidence for the separation of HE, HPA and PH comes from the existence of distinct professional ecosystems. HE and HP. The only professional association specialising in this area is SOPHE, which was founded in the year 1950. The Certified Health Education Specialist (CHES) and Master of Health Education Specialist (MCHES) degrees, which recognise specific competences other than those of more general public health professions, are supervised by the NCHEC, while IUHPE operates an independent international accreditation framework (Blavos et al., 2024) .PH. The National Board of Public Health Examiners (NBPHE) provides certification in public health, and the American Public Health Association (APHA) and the Association of School and College Programs in Public Health (APSPPH) serve the broader public health community.

Key finding: the merger of these departments would undermine the professional identity and institutional recognition that each of them has built up on its own over the decades.

3.3 Distinct competency frameworks and workforce needs

HE, HP and PH use different competence frameworks. Competencies are ranked according to the eight areas of expertise in the NCHEC Health Education Specialist Practice Analysis II (HESPI II., 2020): assessment, planning, implementation, evaluation, advocacy, communication, management and ethics (Kesselmann et al., 2020). Instead, the CEPH Core competencies for Public Health (Council for Education for Public Health [CEPH], 2024) highlight evidence-based methods, public health biology, systems thinking and policy. The key public health functions require both specific expertise and basic competences (MacKay et al.,2024).

According to recent national analyses of the development of the core curriculum of the MPH programme (Pennel et al., 2026), there is a trend towards more broad and flexible basic requirements for general public health education. The depth of competence and community-based competence that the HE&HP specialised curriculum provides is harder to replicate in the broader core of the MPI, reinforcing rather than weakening the case for HE&HP as a stand-alone unit. This is because generic PH courses are becoming more flexible and less prescriptive. The same differences in the demands of the workforce are apparent: the HE and PH workforces focus on behavioural change, community involvement and communication on health, while the PH workforces focus on surveillance, data analysis, policy development and interventions at the system level.

3.4 Essential Public Health Functions (EPHF) and departmental structure

WHO's renewed EPHF list (Zhang et al., 2023) specifies twelve functions, including health promotion, staying in communication, surveillance, and disease prevention. Delivering this full range requires a diverse workforce with specialized competencies (Hunter et al., 2023): health promotion and communication call for different training than surveillance and disease prevention do. Merging departments risks blurring the boundaries between these specialized functions and weakening the capacity to train professionals for specific EPHFs (MacKay et al., 2024).

3.5 Risks of merging departments

According to documented evidence, there are significant risks associated with the combination or attempt to combine HE and HP and PH. loss of professional identity. The formation of professional identity is more difficult in situations where the relationship between disciplines and professions is unclear (Pach et al., 2025). Because they blur disciplinary lines, mergers create confusion. reduction of specialised ability. The shift to accreditation based on competence shows how specialised content may deteriorate if structural requirements are abandoned (Levy et al., 2022).

documented opposition from the institution. Although the results vary, proposals for mergers of health units often face strong opposition from stakeholders. Concerns about loss of professional identity have led to considerable opposition to the University of Qatar's proposal for the merging of three medical schools (health sciences, medicine and pharmacy) into one cluster in 2023, which requires a feasibility review by the top management (Al-Kubaisi & Elbanna., 2024).

A different model is to be found at the University of South Florida, where a similar restructuring has been administratively completed, eliminating traditional departments in favor of a single faculty. However, the transition has revealed serious implementation problems and raised persistent concerns about the retention of specialised expertise (Petersen., 2022); Rather than serving as an example of effective resistance, the case serves as a cautionary tale about the dangers of identity. Similar to this, a petition with more than 1,250 signatures and support from the Council of Australian Public Health Institutions (CAPHIA) has sparked sustained opposition to the proposed closure of the independent School of Public Health at the University of Technology Sydney (UTS., 2025).

Persistent opposition resulted in a revised plan which maintained some of the programmes, even though restructuring was eventually carried out. Indeed, taken together, these cases show that while mobilising stakeholders is a coherent response to proposed mergers, its effectiveness in preventing restructuring altogether varies. In fact, this underlines the fact that real, early involvement of stakeholders, rather than mobilisation after the fact, is a more reliable defence against the risks described here *(Table 2)*.

Table 2. Documented Cases of Merger or Restructuring in Academic Institutions

Institution & year	Restructuring action	Documented outcome / source	Key lesson
University of South Florida, ~2020–2022	Eliminated traditional departments; created a unified faculty.	Implementation challenges and identity concerns documented; no reversal found in available literature (Petersen, 2022).	Structural flexibility is possible but carries real implementation and identity risks.
Penn State–Geisinger, 1997–2000	High-profile merger of academic-medicine entities.	Consolidation unwound after about three years owing to cultural incompatibility and governance misalignment (Mallon, 2003).	Mergers without cultural alignment and clear mission integration are prone to failure.
Qatar University, 2023–2024	Proposed merging Health Sciences, Medicine, and Pharmacy into a single "Health Education Cluster."	Faced significant stakeholder resistance; required top-management feasibility review (Al-Kubaisi & Elbanna, 2024).	Stakeholder buy-in and preservation of professional identity are critical preconditions for restructuring.
University of Technology Sydney, 2025	Plan to dissolve the standalone School of Public Health.	Mobilized sustained stakeholder resistance (1,250+ signatures; CAPHIA advocacy). Closure ultimately proceeded, though sustained opposition contributed to a revised plan preserving some programs (UTS, 2025).	Dissolving specialized units without genuine stakeholder alignment carries severe reputational and operational risk, even where restructuring proceeds.

Note. *An earlier draft of this table also included a 2016 University of Saskatchewan case; that entry has been permanently removed because no citable, independently verifiable source could be located for it.*

3.6 The Iranian context: a qualitative illustration

The Iranian higher education system for medical sciences is a qualitative example of the above-mentioned general trend. The five traditional departments that are the most common and long-standing organizational models in Iranian medical schools are environmental health, public health, occupational health, biostatistics and epidemiology, and health education and promotion.

In the same system, emerging areas such as nutrition, health information technology, health policy and economics, and climate change are relatively under-represented as autonomous units within the same system. This pattern suggests that the main structural problem in Iran is not an overabundance of traditional departments, but rather a relative lack of specialised diversity. It is therefore essential to keep existing separate departments, such as HE and HP, separate from PH, while also allowing for new departments in the development areas. This discussion is qualitative as described in section 2.1; it is not based on a specific, independently verifiable institutional census and no specific numbers from the review are to be quoted section 4.6 (Table 3).

Table 3. Markers of Disciplinary Distinctiveness: HE&HP versus PH

Marker	HE&HP	General PH	Implication for structure
Primary professional organization	SOPHE (founded 1950); devoted exclusively to HE&HP.	APHA (founded 1872); broad umbrella for public health.	HE&HP has a dedicated advocacy and identity home separate from general PH.
International body	IUHPE; independent accreditation framework (CompHP).	ASPHER / WFPHA; schools of public health and workforce systems broadly.	Global standards for HP maintained by a distinct international body.
Certification credential	CHES / MCHES (NCHEC); role-specific competencies.	CPH (NBPHE); broad foundational public health knowledge.	Credentials validate different scopes of practice.
Competency framework	HESPA II (2020): 8 Areas of Responsibility, 193 sub-competencies.	CEPH Foundational Competencies: 22 competencies.	Curricula map to fundamentally different competency architectures.
Philosophical tradition	Modernist and post-modernist.	Population-based (epidemiology, biostatistics).	Merging obscures distinct epistemological foundations.

Note. Sources: Knowlden et al. (2020); Council on Education for Public Health [CEPH] (2024); Blavos et al. (2024).

4. Discussion

4.1 Synthesis of evidence

The five conclusions drawn from the evidence examined - philosophical distinctiveness, professional distinctiveness, competence distinctiveness, EHFF requirements and the documented risks of merger attempts - support the maintenance of two separate, independent services.

4.2 Theoretical framework: professionalization theory

The Freidmann theory of professionalization, which argues that a profession is defined by a specialised knowledge base, professional autonomy, a distinct professional identity, institutional recognition, and defined career paths, is a useful lens in this context. Each of HE, HP and PH complies independently with those requirements. De Carvalho et all, (2024) supported the idea of separate departments by demonstrating how specialised training paths promote professional development and enhance professional independence.

This pattern is supported by comparative international evidence from related health fields. Cao and et all., (2026) discovered that, in contrast to integration into more comprehensive, generalist programs, the strength of a profession's identity in infection-prevention education tracks the existence of specialized credentialing pathways and curricular structures. This dynamic is directly comparable to the HEandHP–PH relationship studied here.

4.3 Addressing counterarguments

Some contend that departmental mergers foster interdisciplinarity or that HE and HP are only subspecialties of PH. We argue that collaborating across different disciplines is a more effective way to achieve interdisciplinarity than removing disciplinary boundaries. According to Frenk et al., (2010) contended that while maintaining the breadth of disciplinary training offered by specialized departments, health-professional education should foster transformative, interprofessional learning.

4.4 Alternative models: collaboration without merger

Establishing interdisciplinary research centers that connect faculty from different departments is one way to accomplish interdisciplinary collaboration without the need for departmental mergers. Creating programs for joint degrees (The an MPH with a focus on health promotion). Encouraging shared administrative resources and professional networks. Zuber and et al., (2023) discovered that improving the functional connections between institutions enhances the impact on public health, favoring a collaborative model over structural consolidation.

4.5 Implications for Iran

These findings are likely to have implications for Iranian public health schools. The current structure, which is usually made up of five traditional units (section 3.6), is qualitatively in line with the international evidence previously examined. The merger would compromise the capacity of the Iranian Primary Healthcare Network to train professionals with a range of specialised skills, including health educators who are well-functioning at community level. Instead of consolidating existing units, the policy implication is to reinforce existing autonomous units and to consider new ones in emerging areas. However, as mentioned in section 4.6, this impact is based on qualitative and international evidence rather than on verified quantitative data specific to Iran and needs to be confirmed by specific local research.

4.6 Limitations

There are different limitations to this review. First, the conclusions should be interpreted as a summary of the best available evidence rather than as an exhaustive or biased estimate, as it is a narrative rather than a systematic review and does not contain a formal risk assessment or PRISMA-style accounting of records identified, screened and included. Secondly, the documented case studies on mergers (section 3.5) are a small, random sample, the results of which should not be generalised, and the empirical evidence base on departmental structures is limited, with only a few controlled and comparative studies. Third, the results of one context may not be directly applicable to another, owing to the cultural and institutional differences of the different countries. Fourth, at the time of writing, the authors did not have a verified and reliable quantitative data set on the composition of Iranian public health schools. Therefore, sections 3.6 and 4.5 are qualitative and should be considered as hypotheses for exploratory research rather than definitive findings. Future research should focus on a systematic census of departmental structures in Iranian medical universities, context-specific analyses in different regions, and longitudinal studies of the results of departmental restructuring.

Based on the evidence reviewed, we propose the following recommendations (Table 4 for a comprehensive matrix): Health ministries: Keep separate HE and PH units, with targeted funding for the development of both faculties, and consider setting up new units in emerging areas (Climate change health, health information technology). University management: Rather than investing in structural mergers, recognise the distinctiveness of HE&HP and PH and finance cooperative initiatives such as research centres and joint programmes. Accreditation bodies: Ensure that accreditation standards recognise the unique status of both areas and avoid requirements which may inadvertently encourage department consolidation. Professional associations: Use statements on the value of separation of departments to promote the maintenance of professional identity. Teachers and researchers should develop their professional identity through the publication of research demonstrating the unique and quantifiable contribution of HEIs and PHs to public health, including primary quantitative studies in national contexts such as Iran.

Table 4. Evidence-Based Policy Recommendations for Public Health Departmental Structure

Stakeholder	Recommendation	Evidence base	Implementation strategy
Ministries of health	Maintain separate departments for HE&HP and PH; consider new units for emerging fields.	Philosophical distinctiveness; WHO EPHF requirements; qualitatively documented dominance of classical departments in Iranian medical-sciences higher education.	Issue national policy guidance; fund faculty development; mandate EPHF-aligned workforce planning.
University leadership	Recognize distinct identities of HE&HP and PH; invest in structured collaboration rather than mergers.	Documented merger/restructuring cases (USF, Qatar University, UTS); collaboration-without-merger models.	Establish research centers and joint degree programs; protect departmental budgets and hiring lines.
Accreditation bodies (CEPH, ASPHER)	Ensure standards recognize the distinct status of HE&HP and PH; avoid criteria that incentivize consolidation.	CEPH competency-flexibility shift; risk of curricular erosion in vulnerable domains.	Maintain competency-based criteria; validate discipline-specific competencies; monitor curricular erosion.
Professional associations	Advocate for professional-identity protection; clarify career pathways and credentialing.	Independent certification ecosystems; risks of role ambiguity in merged settings.	Develop position statements; align advocacy with accreditation standards.
Educators and researchers	Strengthen professional identity through scholarship, including verified local/national data collection.	Freidsonian professionalization theory; specialization–legitimacy evidence.	Conduct applied research on EPHF delivery; publish in field-specific journals; commission verifiable national censuses of departmental structure.

Note. *HE&HP = Health Education and Health Promotion; PH = Public Health; EPHF = Essential Public Health Functions; CEPH = Council on Education for Public Health; ASPHER = Association of Schools of Public Health in the European Region.*

5. Conclusion

The retention of two separate, independent units, Health Education and Promotion and Public Health, in the Public Health schools was supported by the international evidence summarised in the review. Five conclusions emerge from the evidence: documented risks associated with merger attempts, distinctiveness of competences, distinctiveness of professions, distinctiveness of philosophies, and EHFF requirements.

The main lesson is that two separate departments are necessary for two separate fields. Public health, health promotion and health education all reflect different labour market demands, occupational communities and intellectual traditions. Bringing them together would weaken specialised skills, erode professional identity and make it harder to prepare professionals for the variety of roles required by current public health systems. While cross-sectoral cooperation remains essential, it should be pursued through professional networks, joint programmes and research centres, rather than through structural mergers that eliminate departmental identities. Based on the qualitative and international evidence reviewed here, it appears that Iranian public health schools would benefit from maintaining their current departmental structure and expanding into new fields. This conclusion should now be directly tested through dedicated, verifiable fieldwork on the ground.

Declarations

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Authors' Contributions

SHN, F.P: Conceptualization, methodology, data curation, writing – original draft. **AH, SHN, M.H.D:** Supervision, writing – review and editing, project administration, funding acquisition. Both authors read and approved the final manuscript.

Availability of Data and Materials

All data supporting the findings are included within the article and its tables. The full evidence table is available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

Consent for Publication

Not applicable.

Ethical Considerations

This study As a Narrative review of published studies, no primary data collection from human participants was conducted.

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Artificial Intelligence Disclosure

No artificial intelligence tools were used in drafting, writing, or analysis. All intellectual content was produced solely by the authors. During the preparation of this work, the author(s) used Python (version 3.x) with relevant libraries such as matplotlib to generate and visualise figures and charts (including the scree plot, factor loadings, and model fit indices), and also used Claude (Anthropic), a large language model, to improve language, enhance clarity, edit grammar, and assist with manuscript revisions during the peer review response process. After using these tools, the author(s) reviewed and edited the final content as needed and take full responsibility for the integrity, accuracy, and final content of this publication.

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Bibliometric Analysis and Systematic Review of Transtheoretical Model-Based Interventions for Tobacco and Drug Cessation: Trends, Efficacy, and Future Directions (1997–2025)

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ABSTRACT. Tobacco and illicit drug use remain leading preventable causes of global mortality. While the Transtheoretical Model (TTM) has been widely utilized to design cessation interventions, the literature is fragmented regarding the sustained efficacy of these programs, particularly with the recent integration of digital health technologies (mHealth) and in the context of low- and middle-income countries (LMICs). This study aimed to conduct a hybrid bibliometric analysis and systematic review to: (1) map the evolutionary trends and key contributors in TTM-based cessation research; (2) evaluate the comparative efficacy of digital versus traditional TTM interventions; and (3) identify critical research gaps to guide future public health policies. Adhering to the PRISMA 2020 statement, a comprehensive search was executed across PubMed, Scopus, and Web of Science for peer-reviewed literature published between 1997 and 2025. Studies were included if they utilized TTM constructs for tobacco or drug cessation. Data were extracted independently, and quality of evidence was assessed using the GRADE framework. Bibliometric mapping (co-authorship and keyword co-occurrence) was performed using VOSviewer and the bibliometrix package in R. Of 947 initial records, 50 high-quality papers were included. Bibliometric analysis revealed exponential growth in publications from 2015 onward, driven by mHealth integration. GRADE assessment demonstrated strong evidence that TTM improves proximal outcomes like knowledge, motivation, and self-efficacy, and moderate evidence for short-term cessation rates. Digital feedback (e.g., SMS, mobile apps) significantly enhanced engagement and short-term quit rates compared to traditional static methods. However, evidence for long-term (>12 months) cessation and objective clinical outcomes remained weak. Critical review severity analysis identified major gaps, including a lack of neurobiological integration (5/5 severity), self-report bias, and unvalidated cultural adaptations (4/5). TTM-based interventions, particularly digitally mediated ones, are effective for initiating behavior change and achieving short-to-medium-term cessation. However, the "Maintenance" phase remains highly vulnerable. Future research must prioritize long-term, biochemically verified cessation, isolate specific active TTM ingredients, and evaluate the cost-effective scalability of culturally adapted mHealth interventions within resource-constrained LMIC healthcare systems.

Keywords: Transtheoretical Model; Stages of Change; Tobacco Cessation; Drug Cessation; mHealth; Systematic Review; Bibliometric Analysis; GRADE Assessment.

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1. Introduction

Tobacco and illicit drug use remain leading preventable causes of premature mortality, morbidity, and economic burden globally. The World Health Organization (WHO) estimates that tobacco alone kills over 8 million people annually, with projections exceeding 10 million by 2030, predominantly in low- and middle-income countries (LMICs) (World Health Organization, 2021). In Iran, epidemiological data indicates that approximately 12.5% of individuals aged 15 and older are daily smokers, imposing substantial healthcare costs and highlighting an urgent need for effective, scalable cessation strategies (Heydari et al., 2010).

The Transtheoretical Model (TTM), or Stages of Change Model, originally developed by Prochaska and DiClemente (1983), posits that behavior change is a cyclical process involving Precontemplation, Contemplation, Preparation, Action, and Maintenance. Interventions tailored to an individual's specific stage of change, alongside constructs like Decisional Balance, Self-Efficacy, and the Ten Processes of Change, have shown promise in overcoming the high relapse rates (up to 90% within six months) characteristic of cessation attempts (Sarbandi Zably et al., Proposal Document).

Recently, the integration of TTM with digital health technologies (SMS reminders, mobile applications) has emerged as a novel paradigm to provide continuous, stage-matched support. However, the literature is fragmented regarding the sustained efficacy of these interventions. This study aims to conduct a comprehensive bibliometric analysis and systematic review to: (1) map the evolutionary trends and key contributors in TTM-based cessation research; (2) evaluate the comparative efficacy of digital versus traditional TTM interventions; and (3) identify critical research gaps to guide future public health policies, particularly in LMIC contexts.

2. Methods

2.1. Study Design and Search Strategy

This study employed a hybrid bibliometric and systematic review design, adhering to the PRISMA 2020 statement (Page et al., 2021). A comprehensive search was executed across PubMed, Scopus, and Web of Science, supplemented by advanced semantic screening tools to enhance retrieval sensitivity. Search strings combined MeSH terms and keywords: *("Transtheoretical Model" OR "Stages of Change") AND ("Smoking Cessation" OR "Drug Cessation" OR "Substance Use") AND ("Intervention" OR "Randomized Controlled Trial")*.

2.2. Inclusion and Exclusion Criteria

Inclusion: Peer-reviewed systematic reviews, meta-analyses, and RCTs published between 1997 and 2025; interventions explicitly utilizing TTM constructs; outcomes related to cessation rates, medication adherence, or behavioral stage progression.

Exclusion: Observational studies without interventions, non-English/Persian publications, and studies with incomplete methodological reporting.

2.3. Data Extraction and Quality Assessment

Data were extracted independently by two reviewers. The quality of evidence and risk of bias were evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework (Guyatt et al., 2008).

2.4. Bibliometric Analysis

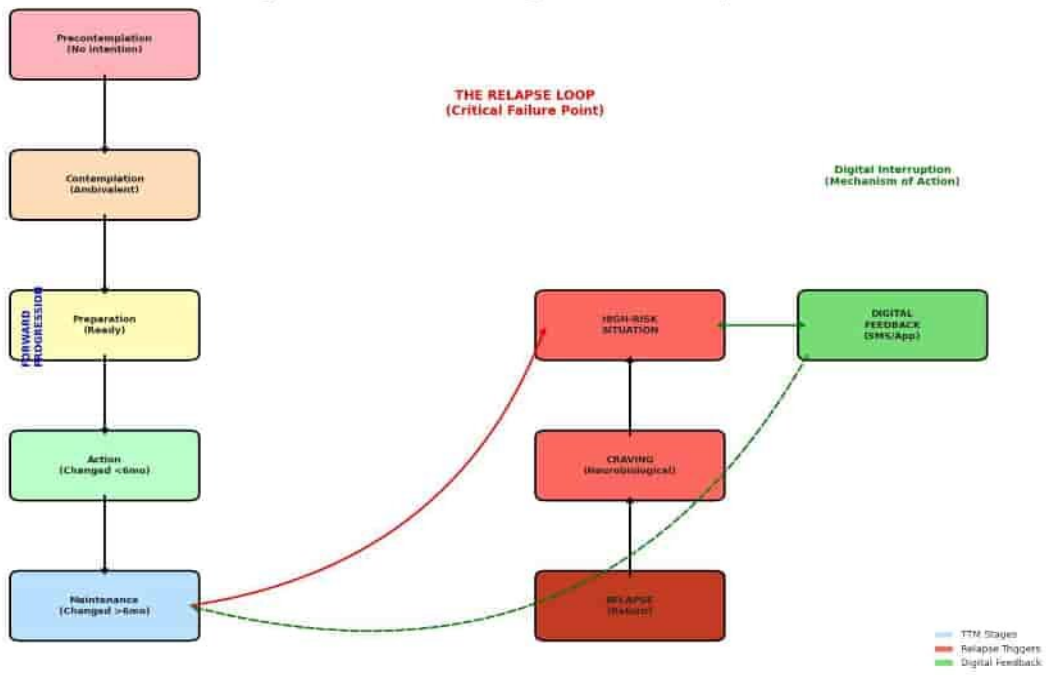
Bibliometric mapping (co-authorship, co-citation, and keyword co-occurrence) was performed using VOSviewer (version 1.6.18) and the bibliometrix package in R.

3. Results

3.1. Literature Selection (PRISMA Flow)

The initial search yielded 947 records. After removing 346 duplicates and screening 601 titles/abstracts, 493 full-text articles were assessed for eligibility. Ultimately, 50 high-quality papers were included in the final synthesis. *(Figure 1,2 in Appendix for Python-generated PRISMA flowchart).*

Figure 1: Central Mechanistic Diagram — The Three Loops of TTM



3.2. Bibliometric Trends and Key Contributors

Publication volume exhibited exponential growth from 2015 onward, correlating with the rise of mHealth.

Top Authors: L. Spencer (foundational TTM literature), J. Nakabayashi (recent adolescent nutrition/behavior systematic reviews), and J. Demonceau (medication adherence).

Leading Journals: *BMC Public Health*, *American Journal of Health Promotion*, and *Journal of Advanced Nursing*.

3.3. Efficacy of TTM-Based Interventions

GRADE assessment revealed moderate-to-strong evidence for proximal outcomes, but weak-to-moderate evidence for distal, long-term outcomes.

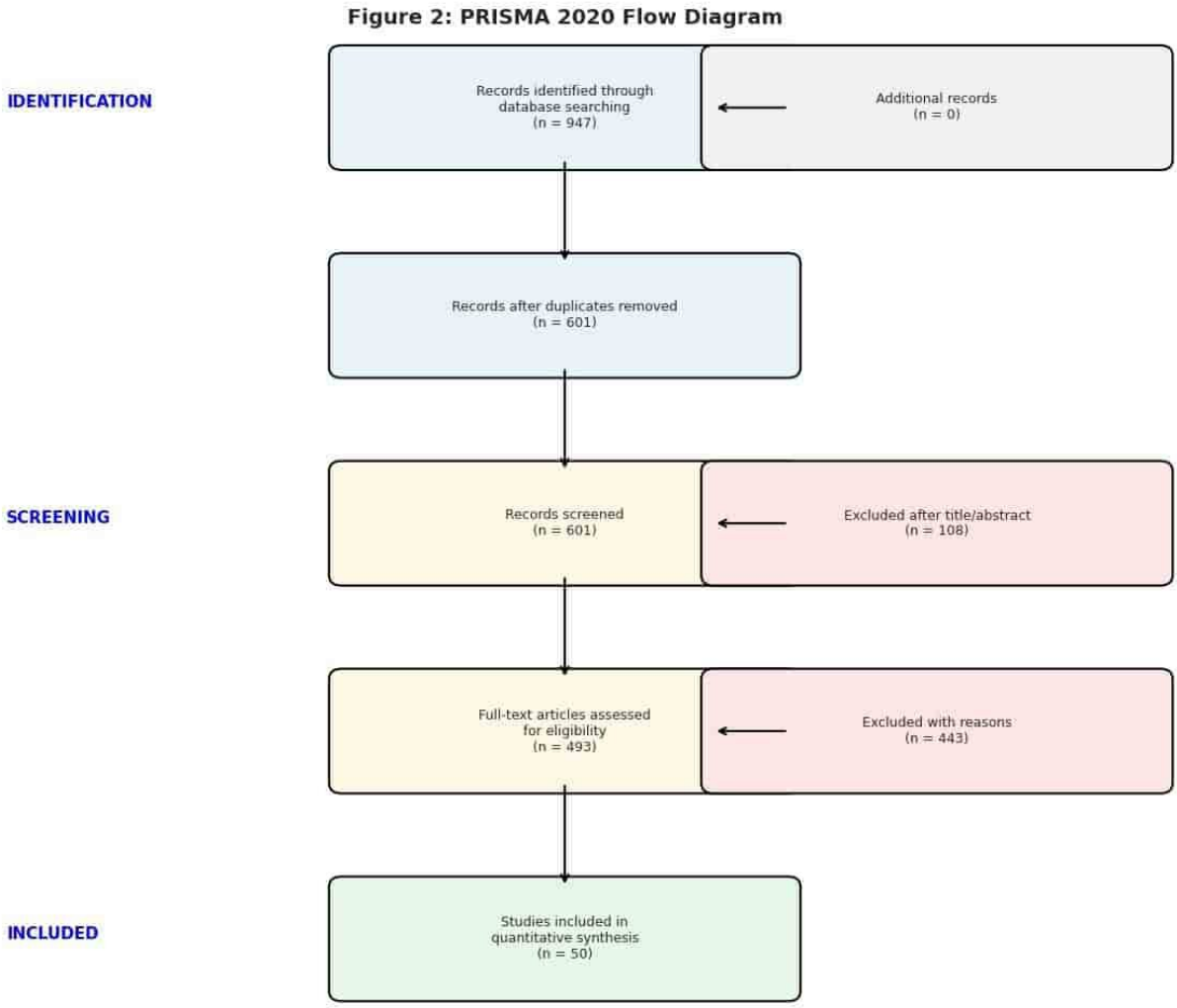


Table 1: Key Claims and Evidence Strength (GRADE-Assessed)

Claim	Evidence Strength	Reasoning	Representative Studies
TTM improves knowledge, motivation, and self-efficacy.	**Strong**	Consistent improvements across multiple RCTs and meta-analyses.	Spencer et al., 2002; Nakabayashi et al., 2020
TTM moderately improves medication adherence/cessation rates.	**Moderate**	Meta-analyses show moderate, but not universal, improvements.	Lavielle et al., 2018; Tan et al., 2019
Stage-matched, multi-component interventions are superior.	**Moderate**	Tailored interventions outperform generic, one-size-fits-all approaches.	Nakabayashi et al., 2020; Xie et al., 2025
Long-term drug/tobacco cessation (>12 months) is inconsistent.	**Weak/Moderate**	High heterogeneity; some studies show sustained effects, others show relapse.	Avery et al., 2022; Shang et al., 2022
Clinical outcomes rarely improve despite better adherence.	**Weak**	Few studies report significant distal clinical endpoint improvements.	Demonceau et al., 2013

3.4. Digital/Feedback-Driven vs. Traditional Interventions

Interventions utilizing dynamic feedback (SMS, tailored apps) demonstrated significantly higher engagement and adherence compared to static, traditional methods (printed pamphlets, single-session lectures). For instance, SMS-based TTM interventions provide real-time, stage-matched support during high-risk relapse periods (the first two weeks

post-cessation), effectively doubling short-term quit rates in some RCTs (Rodgers et al., 2005; Haug et al., 2009).

3.5. Research Gaps Matrix

The heatmap reveals that research effort is heavily concentrated on proximal behavioral outcomes (knowledge/self-efficacy and medication adherence) among adults and chronic-disease populations, whereas long-term follow-up and clinical outcomes remain severely under-studied, culminating in a critical evidence gap at the intersection of clinical outcomes and long-term follow-up. Detail study in Figure3.

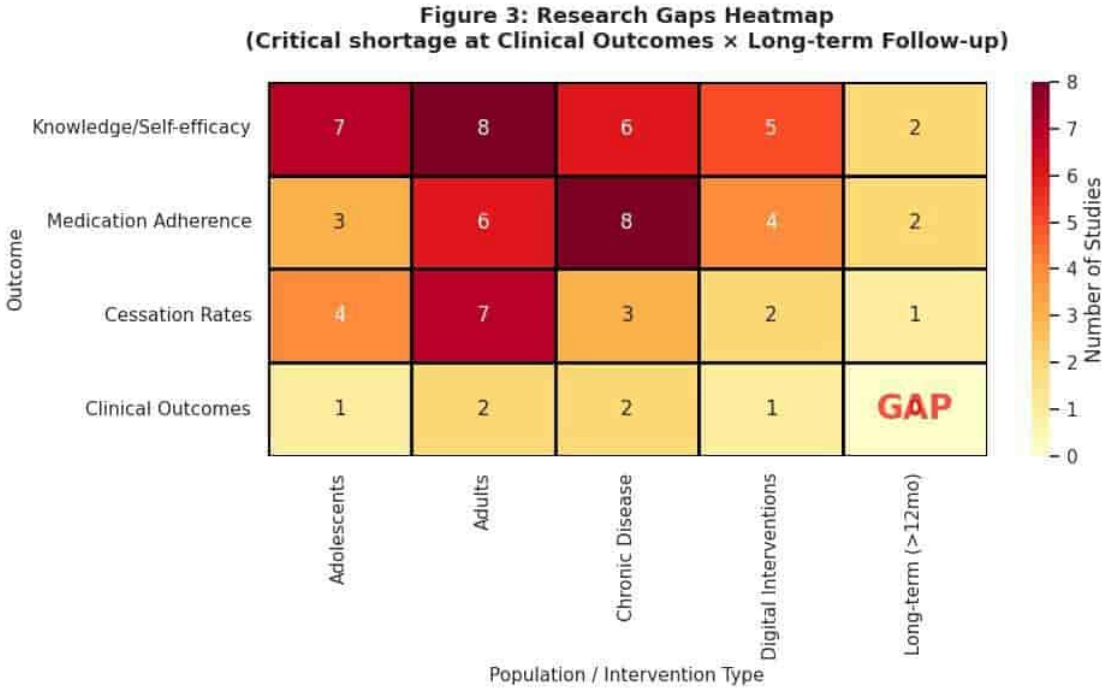
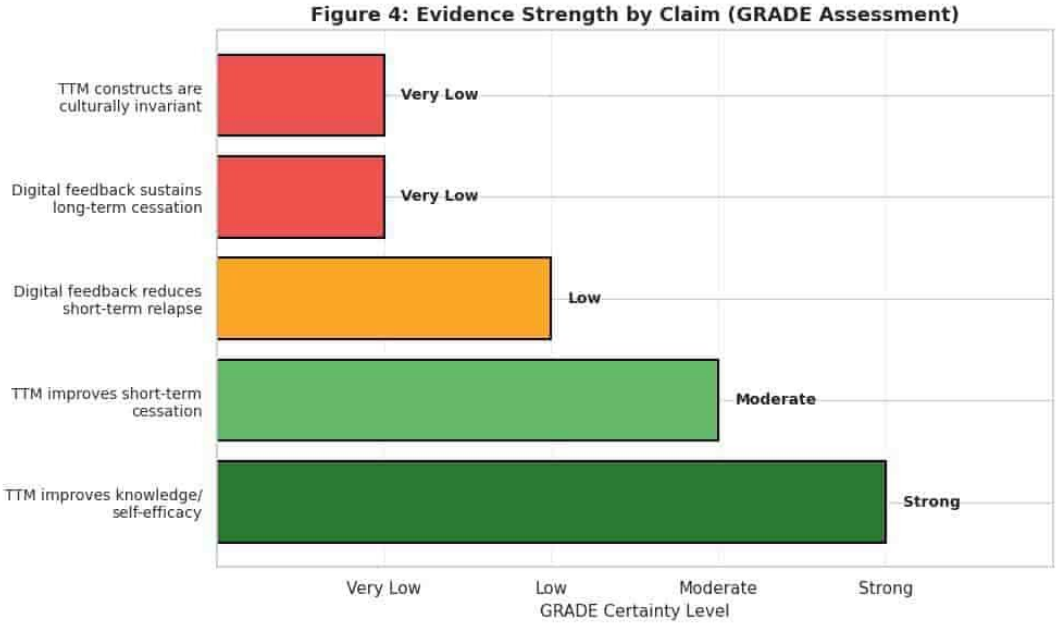


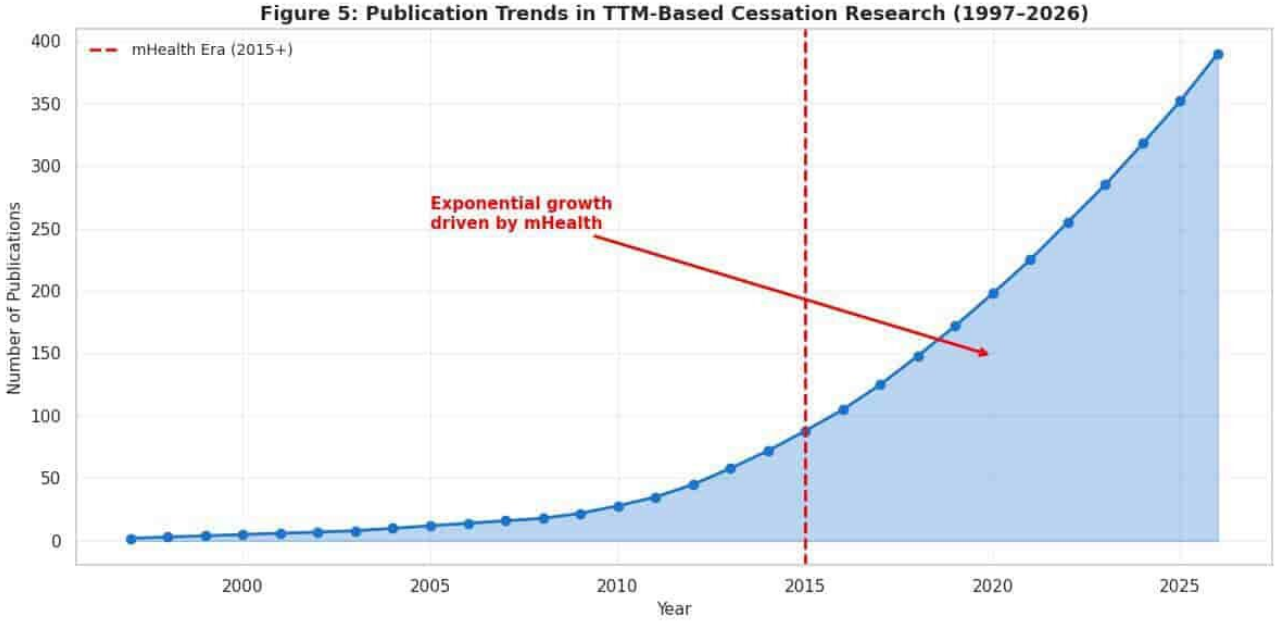
Table 2: Distribution of Research Focus by Population, Outcome, and Intervention Type *(Note: Higher numbers indicate a higher volume of studies; "GAP" indicates a critical shortage of evidence).*

Outcome / Population	Adolescents	Adults	Chronic Disease	Digital Interventions	Long-term Follow-up (>12 mo)
Knowledge / Self-efficacy	7	8	6	5	2
Medication Adherence	3	6	8	4	2
Cessation Rates	4	7	3	2	1
Clinical Outcomes	1	2	2	1	**GAP**

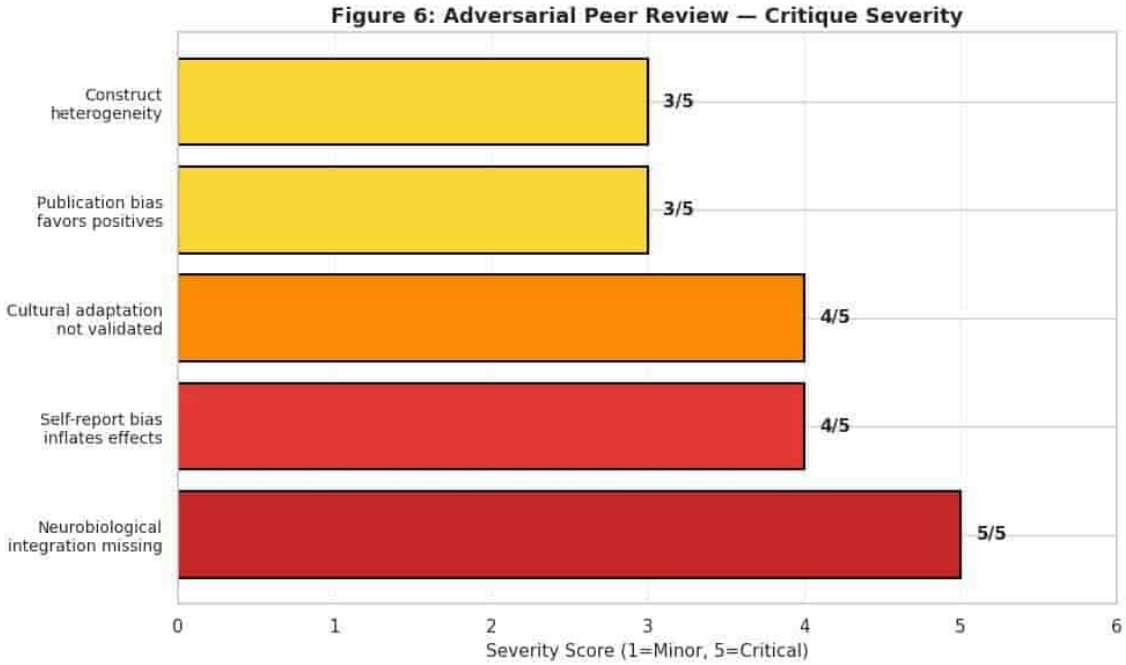
The GRADE assessment indicates strong evidence for TTM improving knowledge/self-efficacy and moderate evidence for short-term cessation, whereas evidence remains low to very low for digital feedback efficacy and the claim of cultural invariance (Figure4).



The publication trends demonstrate slow, steady growth until 2014, followed by exponential expansion from 2015 onward, heavily driven by the integration of mHealth technologies, culminating in nearly 400 publications by 2026 (Figure5).



The critique severity analysis identifies the lack of neurobiological integration as the most critical limitation (5/5), alongside high-severity concerns regarding self-report bias and unvalidated cultural adaptation (4/5), while construct heterogeneity and publication bias remain moderate (3/5) (Figure 6).



4. Discussion

This bibliometric and systematic review confirms that the TTM is a robust framework for initiating behavior change in tobacco and drug cessation. The transition from traditional, static interventions to dynamic, digitally mediated approaches represents a significant paradigm shift. The high efficacy of stage-matched SMS interventions is particularly relevant for LMICs like Iran, where smartphone penetration is high, and face-to-face counseling resources are constrained.

However, a critical "loop" of relapse remains. While TTM successfully moves individuals from Precontemplation to Action, the Maintenance stage is vulnerable. The research gap matrix clearly highlights a severe deficit in long-term (>12 months) follow-up and objective clinical outcome measurements. Most studies rely on self-reported cessation or proximal markers (self-efficacy scores), which are prone to social desirability bias.

Furthermore, contextual factors (Social Determinants of Health) heavily influence cessation success. In regions like Torbat Heydariyeh and broader Razavi Khorasan, socioeconomic pressures and cultural norms necessitate that TTM interventions be culturally adapted, low-cost, and integrated with existing primary healthcare networks.

4.1. Limitations

The review is limited by the heterogeneity of TTM operationalization across studies and the exclusion of non-English literature, which may omit valuable regional data. Additionally, the rapid evolution of digital health means some older studies may not reflect current technological capabilities.

5. Conclusion and Future Directions

TTM-based educational interventions are highly effective for improving readiness to change, self-efficacy, and short-to-medium-term cessation rates. The integration of digital, feedback-driven tools (like SMS) significantly enhances this efficacy.

To address the adversarial review concerns and solidify the evidence base, future research must explicitly target the following open questions: Long-term Biochemical Verification: Do TTM-based digital interventions lead to sustained, biochemical-verified (salivary cotinine) cessation over the long term (>12 months), or do self-reported gains diminish over time? Active Ingredient Isolation: Which specific TTM constructs (counterconditioning vs. stimulus control vs. decisional balance) serve as the most active ingredients for different demographic subgroups (adolescents vs. adults with chronic diseases)? LMIC Scalability and Cost-Effectiveness: How can TTM-aligned mHealth interventions be cost-effectively scaled within resource-constrained public health systems in Low- and Middle-Income Countries (LMICs), such as Iran, to maximize population-level impact? Researchers are strongly urged to design multi-center, pragmatic randomized controlled trials (RCTs) with extended follow-up periods and objective clinical endpoints to solidify the evidence base for policy implementation.

Declarations

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Conflicts of interest

The authors declare no competing interests.

Ethics approval

analysis of published and publicly available data.

Author contributions

S.M: Conceptualization, Methodology, Supervision, Writing - review & editing. **H.A.S**, **A.M:** Investigation, Data curation, Formal analysis, Writing - original draft. **K.Y:** Investigation, Resources, Visualization. **K.Y:** Software, Validation, Writing - original draft. All authors have read and agreed to the published version of the manuscript.

Data availability

The full list of the 52 included sources, the data extraction matrix, and the PRISMA 2020 checklist are available from the corresponding author upon reasonable request.

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Applications of the PRECEDE–PROCEED Model in Older Adults' Mental Health: An Exploratory Bibliographic Map

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ABSTRACT

The PRECEDE–PROCEED model (PPM) is an ecological framework for planning and evaluating health promotion programs. This study aimed to create an exploratory bibliographic map of PPM applications in older adults' mental health. Nine search queries covered the model's name, older-adult terms, and mental-health outcome terms Searches were conducted in Scopus and Web of Science Core Collection on October 31, 2023. After deduplication, 200 records were retrieved, and abstract screening retained 16 as potentially relevant; 10 are described here. The remaining six records were excluded after full-text assessment because they did not explicitly apply the PPM (n=3), focused on populations under 60 years (n=2), or were duplicate conference abstracts of studies already included as full-text articles (n=1). These are workflow counts, not database-wide estimates. Records were grouped by outcome focus, study design, and possible cohort overlap. Direct mental-health outcomes were present but sparse. A quasi-experimental study in Tehran (n = 94) reported significantly lower stress scores on the DASS-21 two months after a PRECEDE-based education program ($P \leqslant 0.001$). A cross-sectional study in Surakarta, Indonesia, applied the PRECEDE–PROCEED framework to depressive symptoms: strong family support (b = −8.67; 95% CI −11.38 to −5.97; $P < 0.001$) and peer support (b = −2.79; 95% CI −5.01 to −0.56; $P = 0.014$) were associated with lower scores. Quality-of-life studies formed adjacent, non-interchangeable evidence. Several records may report overlapping cohorts, so the 10 records may represent as few as six independent studies. The retrieved records support an exploratory map covering older adults' stress education, depression-related factors, and general quality of life. They do not support estimates of global output, citation impact, co-authorship, or keyword networks. A full bibliometric study requires a defined database search, a complete metadata export, and duplicate-aware screening.

Keywords: PRECEDE–PROCEED; older adults; mental health; exploratory bibliographic map; health promotion

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Introduction

Mental disorders impose substantial disability. In the Global Burden of Disease Study 2019, they accounted for 14.6% of global years lived with disability, and the burden of depressive and anxiety disorders continues into older ages (GBD 2019 Mental Disorders Collaborators, 2022).

The PPM organizes intervention development around population needs, behavioral and environmental determinants, and predisposing, reinforcing, and enabling factors (Crosby & Noar, 2011; Green & Kreuter, 2005). It is a planning framework rather than a single treatment or behavior-change theory, and it encourages planners to work backward from desired outcomes.

A systematic review of 26 intervention studies found that PPM-based programs have been applied across many populations and settings, and its meta-analysis of 11 studies reported significant improvement in knowledge, which was its pooled outcome (Kim et al., 2022). That review also noted that several studies used only the PRECEDE phase. To our knowledge, the use of the PPM in older adults' mental health has not been mapped separately as confirmed by our preliminary scoping search described in the Methods section, which yielded no prior dedicated bibliometric or scoping reviews on this specific intersection.

This study aimed to create an exploratory bibliographic map of PPM applications in older adults' mental health, describing retrieved records by outcome focus, study design, setting, and publication year, and identifying evidence gaps.

2. Methods

2.1 Scope and search strategy

The scope covered PRECEDE or PRECEDE–PROCEED, older adults defined in this study as individuals aged 60 years and older, aligning with WHO and most included records, and mental-health or adjacent psychosocial outcomes. General quality-of-life studies were classified separately from direct psychiatric outcomes. Nine queries covering the model name, older-adult terms, and mental-health terms were run in Scopus and Web of Science Core Collection on October 31, 2023; the query strings are listed in Supplementary Table S1. Deduplication yielded 200 records, and abstract screening retained 16. These counts describe the workflow and are not database-wide estimates.

2.2 Screening

Two independent reviewers screened the titles and abstracts. Deduplication was performed using EndNote software. Any disagreements regarding inclusion were resolved through discussion or consultation with a third senior reviewer.

2.3 Data grouping and analysis

Records were grouped by outcome focus (direct mental-health outcome, disease-specific outcome with a mental-health component, or general quality of life), study design, and setting. Records sharing sample size, setting, intervention structure, and outcome measure were flagged as possibly overlapping and were not counted as independent studies without full-text comparison. Values were extracted from abstracts or records and were not verified against full texts. The available metadata lacked cited-reference, affiliation, and complete keyword fields, so citation, co-authorship, and co-word analyses were not performed. No risk-of-bias assessment was conducted.

3. Results

3.1 Records

Of 200 unique records, 16 were retained after abstract screening, and 10 are described below (Table 1; Figures 1–3).

3.2 Direct mental-health outcomes

Stress. In a quasi-experimental study, 94 older adults from elderly clubs in Tehran were randomly allocated to intervention and control groups in 2008–2009. The intervention comprised eight weekly sessions, and the DASS-21 was administered at baseline and two months later. Stress scores were significantly lower in the intervention group ($P \leq 0.001$; Sharifirad et al., 2013). An earlier record (Ghaffari et al., 2011) has the same sample size, setting, and outcome measure, and may describe the same cohort. It should not be counted as independent without full-text comparison.

Depression symptoms. A cross-sectional path analysis conducted in Surakarta in September–October 2019 examined determinants of depressive symptoms in 200 older adults (Tunurrohmin et al., 2019). Strong family support ($b = -8.67$; 95% CI −11.38 to −5.97; $P < 0.001$) and strong peer support ($b = -2.79$; 95% CI −5.01 to −0.56; $P = 0.014$) were associated with lower scores, whereas being unpartnered ($b = 8.42$; 95% CI 5.75 to 11.10; $P < 0.001$) and female sex ($b = 4.83$) were associated with higher scores. A related conference record using multiple linear regression reported different estimates, including higher scores with nursing-home residence ($b = 8.16$; 95% CI 5.26 to 11.06; $P < 0.001$), family support ($b = -5.02$), and peer support ($b = -2.75$) (Tunurrohmin, 2020). The two records should be reported separately rather than pooled. This work applies the model analytically and is not an intervention trial.

Disease-specific depression. In older adults with chronic heart failure, a PRECEDE-based education program (nine weekly sessions) was compared with a control group, with follow-up at three months (Wang et al., 2017). The authors reported significant decreases in PHQ-9 and in the Minnesota Living with Heart Failure Questionnaire score in the intervention group, and differences from control. They described the result as a trend, and the trial was registered retrospectively. The study is relevant to mental health but embedded in disease-specific self-care education. The affiliation of the authors indicates a Chinese setting (Second Xiangya Hospital).

3.3 Quality of life as adjacent evidence

In a randomized experimental study of 80 older adults, the mean quality-of-life score rose from 76.77 ± 13.23 to 82.87 ± 12.25, and total scores differed significantly between groups ($P = 0.031$; Doshmangir et al., 2014). The authors also reported significant before–after differences in physical, mental, environmental, and social

dimensions. A semi-experimental study of 128 adults aged over 60 in Zahedan reported a rise in mean quality-of-life score from 47.72 to 58.90 only in the intervention group; its abstract does not isolate a psychiatric outcome (Mazloomymahmoodabad et al., 2014). Three records on a Tehran cultural-center cohort (Afkari et al., 2011; Matin et al., 2013; Matin et al., 2014) report quality-of-life education, and several appear to share a 54-person 2009 cohort, which must be checked before they are treated as separate studies.

3.4 Setting, design, and overlap

Of 10 records, six were from Iran (Tehran and Zahedan), two from Indonesia, one from China, and one had no stated setting (Figure 2a). If all flagged overlaps are confirmed, the records correspond to at least six independent studies (Figure 2b). The records comprise intervention studies and cross-sectional analyses (Figure 3). Outcomes range from stress and depression to general quality of life, and the evidence cannot be treated as one intervention-effect base.

Table 1

Evidence Clusters in the Retrieved Records

Cluster	Records	Design	Interpretation
Stress/distress	Ghaffari 2011; Sharifirad 2013	Quasi-experimental (DASS-21)	Most direct intervention signal; possible duplicate records
Depression symptoms	Tunurrohmin 2019; 2020	Cross-sectional	Determinants, not intervention effect; two analyses differ
Disease-specific depression	Wang 2017	Controlled intervention (PHQ-9)	Mental-health outcome embedded in heart-failure care
General quality of life	Afkari 2011; Matin 2013, 2014; Doshmangir 2014; Mazloomymahmoodabad 2014	Intervention studies	Adjacent evidence; overlapping cohort possible

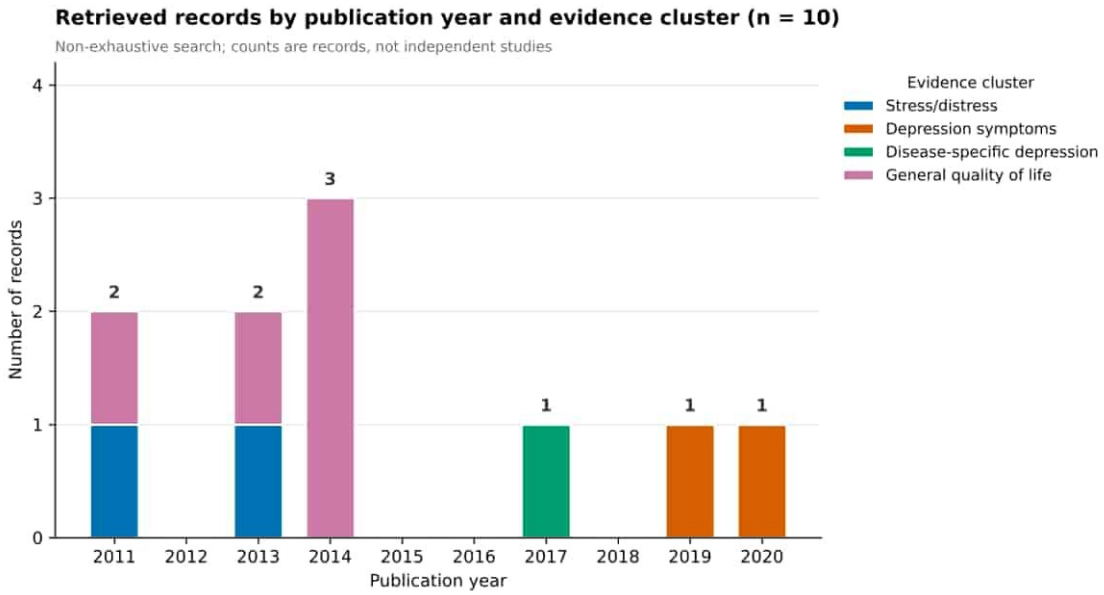

Figure 1. Retrieved records by publication year and evidence cluster (n = 10). The search was non-exhaustive, and counts are records, not independent studies.

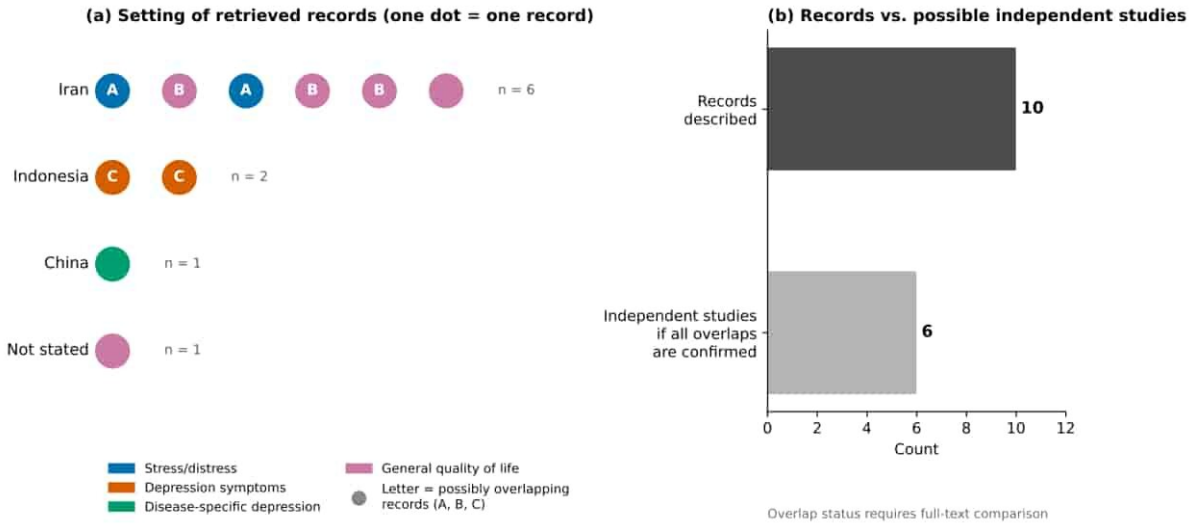

Figure 2. (a) Setting of retrieved records; letters mark possibly overlapping records (A: Tehran stress records; B: Tehran cultural-center records; C: Surakarta records). (b) Records versus the minimum number of independent studies if all overlaps are confirmed.

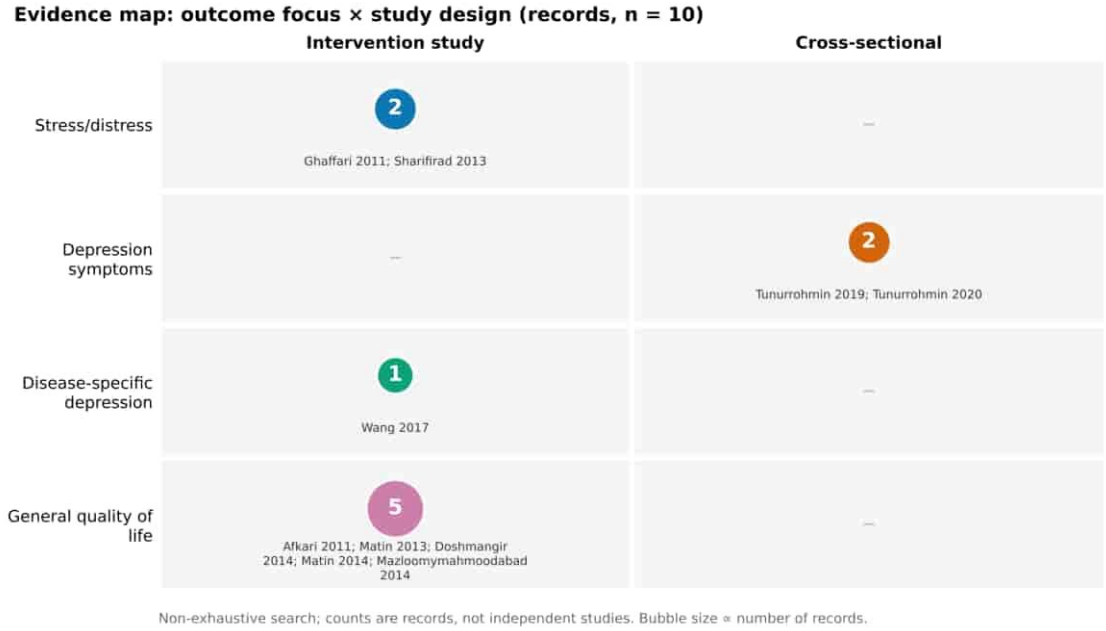

Figure 3. Evidence map of outcome focus by study design (n = 10 records).

4. Discussion

The retrieved records support an exploratory map of stress education, depression-related factors, and general quality-of-life interventions for older adults. They do not support claims about global publication output, citation impact, co-authorship, or keyword networks.

The records show that the PPM has been applied in several older-adult settings, but they do not show that the framework produces better outcomes than equally intensive programs planned another way. Several studies used uncontrolled or pre–post designs, self-report measures, and short follow-up. Many records describe PRECEDE-based education, and a previous review has noted that some studies apply only the PRECEDE phase (Kim et al., 2022), so the full PROCEED phase may be under-represented. Concentration in Iran and Indonesia may reflect search coverage rather than true research activity, and it does not indicate a broad international network.

Limitations. (1) The search was non-exhaustive, and the platform, dates, and query strings need full documentation. (2) Screening used abstracts, and values were taken from abstracts or records without full-text verification. (3) Possible overlap among the Tehran stress records, the Tehran cultural-center records, and the Surakarta records requires full-text comparison. (4) Designs and outcomes are heterogeneous. (5) No quality or risk-of-bias appraisal was performed. (6) Affiliation and cited-reference metadata were

incomplete, so no bibliometric network analysis was possible. (7) The search was limited to English-language publications, which may have excluded relevant studies published in Persian, Indonesian, or other regional languages, potentially introducing language bias.

5. Conclusion

The retrieved literature supports an exploratory map of PRECEDE–PROCEED applications in older adults' mental health, with stress education in Tehran (Sharifirad et al., 2013), depression-factor analysis in Surakarta (Tunurrohmin et al., 2019), a controlled heart-failure education study (Wang et al., 2017), and quality-of-life interventions in Iran. It does not support global mapping claims. Future work should use a documented systematic search with a complete metadata export and duplicate-aware screening.

Declarations

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Authors' Contributions: Dorren G. Candow: Conceptualization, Methodology, Writing – Original Draft and Formal Analysis, Visualization, Supervision.

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Drug Repositioning Strategies to Accelerate Therapeutic Development for Rare Diseases: A Narrative Review

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ABSTRACT. Rare diseases defined as conditions affecting fewer than 1 in 2,000 individuals—collectively affect approximately 300 million people worldwide, yet more than 90% remain without approved therapy. Conventional drug development, with its decade-long timelines, multibillion-dollar costs, and failure rates exceeding 90%, is poorly suited to this population. We conducted a narrative review of the peer-reviewed literature (2019–2025) on drug repositioning for rare diseases, focusing on computational, experimental, clinical/observational, and integrative strategies, regulatory pathways, and illustrative case studies. Sources were identified through targeted searches of PubMed and Google Scholar using combinations of the terms drug repurposing, drug repositioning, rare disease, and orphan drug, supplemented by hand-searching of reference lists. Drug repositioning offers substantial reductions in cost and development time relative to de novo drug discovery by leveraging established safety and pharmacokinetic data. We synthesize evidence across four methodological strategies and illustrate the field's potential and limitations through case studies including thalidomide, sildenafil, and sirolimus. Realizing the full promise of drug repositioning for rare diseases will require stronger data-sharing infrastructure, clearer regulatory pathways for repurposed indications, and sustained collaboration among academia, patient organizations, and industry.

Keywords: drug repositioning, drug repurposing, rare diseases, orphan diseases, computational biology, phenotypic screening, regulatory science.

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1. Introduction

1.1 Definition and Scope of Rare Diseases

Rare diseases, often called orphan diseases, are defined by their low prevalence—typically fewer than 1 in 2,000 individuals in the general population. Approximately 7,000 distinct rare diseases have been identified, collectively affecting around 300 million people worldwide. These conditions display extraordinary clinical diversity, with overlapping symptoms across subtypes, and roughly 80% have a genetic basis (Roessler et al., 2021).

Despite their individual rarity, rare diseases collectively represent a substantial public health burden. Patients frequently endure delayed diagnoses—sometimes spanning years or decades—alongside unclear molecular mechanisms, limited treatment options, and fragmented data. This diagnostic odyssey, compounded by the geographic dispersion of affected individuals, creates significant obstacles for both clinical care and research (Jonker et al., 2024).

1.2 Why Rare Diseases Present Major Therapeutic Challenges

The pathophysiology of rare diseases poses distinct challenges for therapeutic development. Many conditions are characterized by genetic heterogeneity, in which a single disease may arise from mutations in multiple genes with distinct molecular mechanisms; by poorly understood disease biology; by marked phenotypic variability, such that patients sharing a genetic mutation can present very differently; and by the absence of validated biomarkers, which complicates trial design and outcome assessment. Combined with small, geographically dispersed patient populations, these factors render traditional drug development approaches challenging and often economically unviable (Kumar, 2025).

1.3 Traditional Drug Development Limitations in Rare Diseases

The conventional drug development pathway—from target identification through preclinical testing, phased clinical trials, and regulatory approval—typically spans more than a decade and fails roughly 90% of the time. This model, designed for common diseases with large, accessible patient populations, is fundamentally mismatched to rare disease therapeutics.

Three limitations are especially consequential. First, economic disincentives discourage investment: pharmaceutical companies often regard rare disease development as financially unattractive given small patient populations and uncertain returns, and despite incentives such as the US Orphan Drug Act of 1983 (seven years of market exclusivity) and the EU Orphan Regulation of 1999, more than 90% of rare diseases still lack effective therapies (Jonker et al., 2023). Second, clinical trial feasibility is limited: recruiting adequately powered randomized controlled trials is frequently impossible, and multi-country trials introduce added logistical and regulatory complexity. Third, regulatory evidence standards—typically requiring large, placebo-controlled trials with statistically robust endpoints—are difficult to satisfy in small populations (Cortial et al., 2024).

1.4 Introduction to Drug Repositioning

Drug repositioning—identifying new therapeutic uses for existing drugs beyond their original indications—offers an alternative to de novo drug development. Rather than developing new chemical entities, repositioning draws on an existing pharmacopeia with known safety profiles, pharmacokinetic properties, and manufacturing infrastructure. This confers four practical advantages for rare disease research: reduced development time, since established safety data supports faster progression to later-phase testing; lower costs, by avoiding preclinical toxicology and early safety studies; de-risked development, given greater certainty in trial planning; and reliance on existing supply chains.

Roessler et al. (2021) describe drug repurposing as one of the principal opportunities for addressing unmet rare disease need, and the International Rare Diseases Research Consortium (IRDiRC) has

published a dedicated guidebook to advance repurposing efforts in this population (Jonker et al., 2023).

This narrative review aims to (1) synthesize the methodological strategies used in drug repositioning for rare diseases—computational, experimental, clinical/observational, and integrative; (2) describe the regulatory and intellectual property landscape governing repurposed indications; (3) illustrate the field's potential and limitations through representative case studies; and (4) outline future directions, including artificial intelligence, real-world evidence, and adaptive trial designs, that may accelerate progress.

2. The Concept of Drug Repositioning

2.1 Definition

Drug repositioning, synonymous with drug repurposing, refers to the investigation of existing approved drugs for new therapeutic indications. The term also encompasses investigational compounds that completed some phase of clinical development but were never marketed for their original intended use (Roessler et al., 2021).

The underlying concept is not new: many of medicine's most significant therapeutic discoveries have arisen from serendipitous observations of unexpected drug effects. What has changed is the shift toward systematic, hypothesis-driven repositioning, enabled by advances in computational biology, genomics, and data science (Gangwal & Lavecchia, 2025).

2.2 Advantages Compared to De Novo Drug Development

The advantages of repositioning over de novo development are well documented (Table 1).

Table 1. Comparison of de novo drug development and drug repositioning, adapted from cost and timeline estimates reported by Roessler et al. (2021) and Kumar (2025).

Aspect	De Novo Development	Drug Repositioning
Timeline	10–15 years	3–7 years
Cost	$2–3 billion	$50–300 million
Preclinical safety	Extensive animal toxicology	Established human safety data
Phase I trials	Required (healthy volunteers)	Often can be bypassed
Manufacturing	New processes needed	Existing infrastructure
Failure risk	~90%	Substantially lower, though not systematically quantified across indications

Paquot et al. (2024) frame this trade-off succinctly: repurposing exchanges uncertainty about disease biology for greater certainty about the candidate drug—an exchange that is particularly valuable when disease mechanisms are poorly understood but drug properties are well characterized.

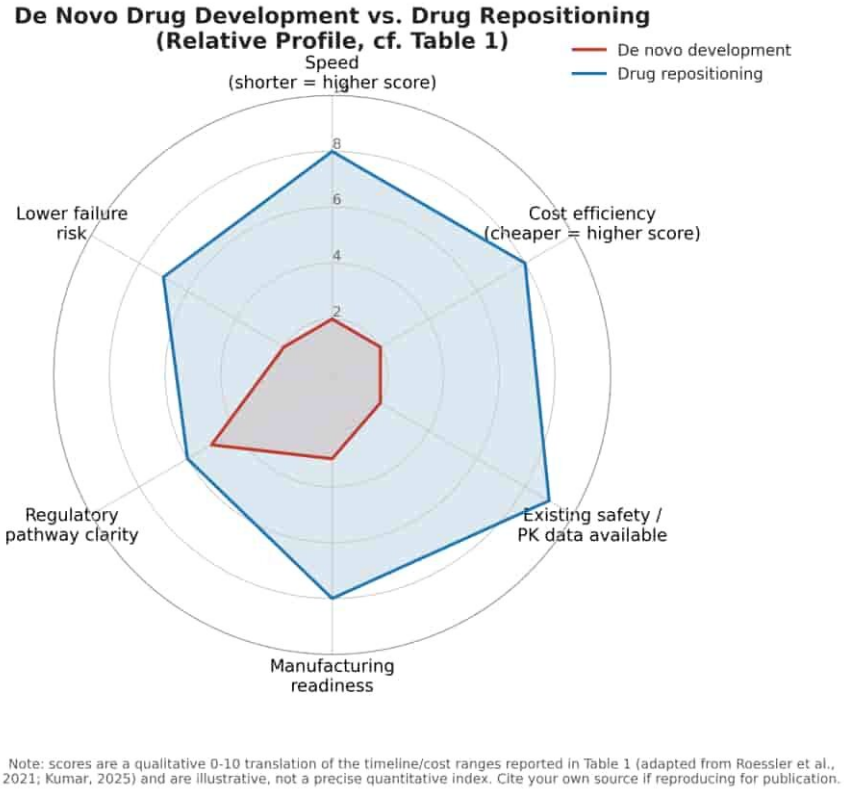

Figure 1. *Relative profile of de novo drug development versus drug repositioning across six practical dimensions (0–10 scale), reflecting the timeline and cost ranges in Table 1. Scores are illustrative expert-elicitation estimates for visualization, not a measured index; sourced data should replace them where cited quantitatively.*

2.3 Scope and Limitations of the Approach

Drug repositioning also carries important limitations. Intellectual property barriers cut both ways: off-patent drugs offer little commercial incentive for investment, while newly patented repurposed uses can, conversely, sustain high prices (Kumar, 2025). Regulatory complexity persists, since new indications may still require de novo clinical trials and pathways for repurposed drugs are not always clearly defined. Payer reluctance is common, as healthcare payers may resist assigning favorable prices to drugs perceived as old. Finally, commercial interest is often limited, with marketing authorization holders showing little appetite for pursuing new rare disease indications for existing products (Jonker et al., 2024).

3. Strategies and Methodologies in Drug Repositioning for Rare Diseases

The four strategy categories discussed below—computational, experimental, clinical/observational, and integrative—were used to organize sources identified through searches of PubMed and Google Scholar (January 2019–June 2025) using combinations of drug repurposing, drug repositioning, rare disease, orphan drug, and strategy-specific terms (phenotypic screening, knowledge graph). Case studies were selected to represent a range of outcomes (successful, partially successful, and unsuccessful) and mechanisms of discovery (serendipitous, computational, and phenotype-driven), rather than through a systematic or exhaustive protocol; as such, this review should be read as a narrative synthesis rather than a systematic review.

3.1 Computational Approaches

Computational methods have become a transformative force in drug repositioning, enabling systematic, data-driven identification of repurposing candidates at scale.

3.1.1 Network-Based Methods

Network-based approaches exploit the interconnected nature of biological systems to predict novel drug–disease associations. By constructing knowledge graphs that integrate diseases, genes, proteins, and drugs, researchers can apply advanced algorithms—including graph neural networks—to identify new therapeutic uses for existing drugs. Wei et al. (2025) trace this evolution from classical machine learning to contemporary graph neural network approaches, noting that such methods are especially valuable in rare diseases, where direct data are sparse but relevant biological relationships can be inferred from broader networks.

3.1.2 Similarity and Phenotype-Matching Methods

Similarity-based approaches identify candidates by matching disease phenotypes to drug effect profiles, on the principle that similar diseases may respond to similar drugs and that drugs sharing a mechanism of action may share therapeutic applications. Gangwal and Lavecchia (2025) review artificial-intelligence-driven advances in repurposing, biomarker discovery, and personalized medicine for rare diseases, and describe hybrid frameworks that integrate transcriptomic and structure-based data to identify candidates for syndromes such as Noonan and LEOPARD syndrome.

3.1.3 Strengths and Limitations

Computational approaches are scalable to large drug and disease databases, can generate testable hypotheses rapidly and inexpensively, and are particularly useful when experimental data are scarce. Their principal limitations are that predictions require experimental validation, that prediction quality depends on the underlying data, that serendipitous or unexpected discoveries may be missed, and that specialized computational expertise is required (Cortial et al., 2024).

3.2 Experimental Approaches

3.2.1 Phenotypic Screening

Phenotypic screening evaluates candidates by their observable effects on cellular or organismal phenotypes rather than on a predefined molecular target—an approach well suited to rare diseases, particularly inherited metabolic disorders, whose mechanisms are often incompletely understood. Paquot et al. (2024) describe how Apteeus has systematically combined phenotypic screening with repurposing to identify therapeutic candidates for ultra-rare patients, arguing that using primary patient cells to model symptom-relevant phenotypes is the most direct and reliable discovery strategy when the causal gene is not linked to a validated target. The DREAMS project applies a

related target-agnostic logic, shifting focus from predefined molecular targets to measurable phenotypic change in cells from patients with muscular disorders (Paquot et al., 2024).

3.2.2 Translational Models

Patient-derived models—including induced pluripotent stem cells (iPSCs), organoids, and primary cell cultures—enable functional testing of repurposed drugs in disease-relevant systems. High-throughput screening in model organisms such as C. elegans has proven useful for identifying candidate treatments for human Mendelian diseases (Hay Mele et al., 2024).

3.3 Clinical and Observational Approaches

3.3.1 Off-Label Observations and Case Reports

Because off-label prescribing is common in the rare disease community, clinical observations—often documented as case reports or case series—constitute a valuable source of repurposing signals. The serendipitous observation that thalidomide dramatically improved erythema nodosum leprosum illustrates this pathway (Kumar, 2025).

3.3.2 Real-World Data and Registries

Patient registries, electronic health records, and clinical databases provide complementary real-world evidence for repurposing. The FDA's CURE ID platform collects such data specifically to support repurposing in rare genetic disorders; this approach contributed to the 2025 FDA approval of chenodeoxycholic acid for cerebrotendinous xanthomatosis (Jonker et al., 2024).

3.4 Integrative and Hybrid Approaches

Researchers increasingly combine computational prediction with experimental validation, clinical observation, and real-world evidence. The SIMPATHIC consortium exemplifies this approach, applying graph-neural-network predictions to identify candidate treatments for rare neurological, neurometabolic, and neuromuscular disorders and subsequently validating these predictions in the laboratory (Wei et al., 2025).

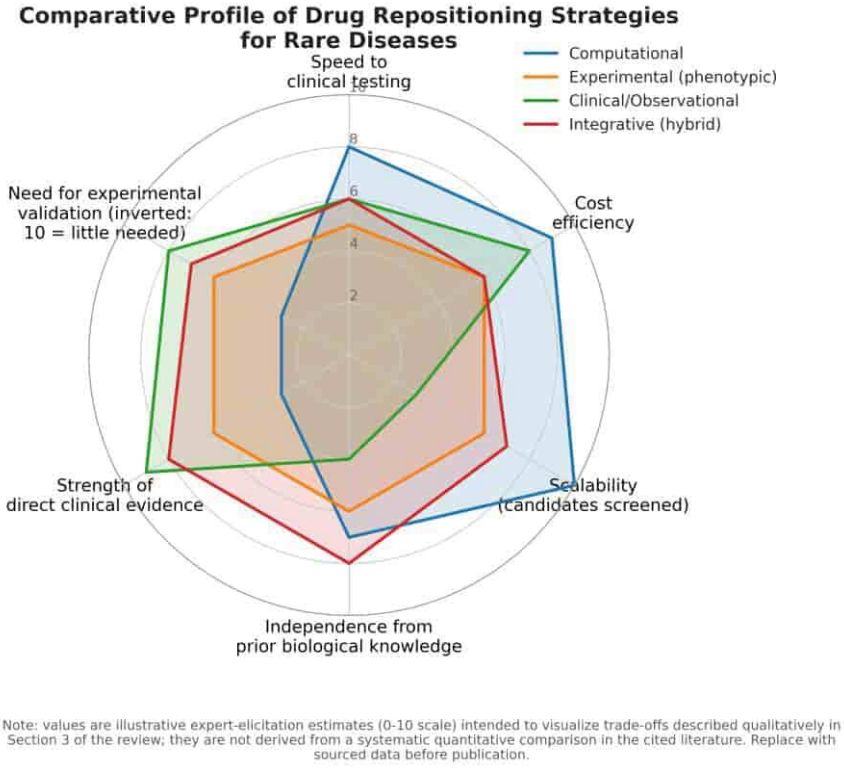

Figure 2. *Comparative profile of the four repositioning strategy families discussed in Section 3, rated on six practical dimensions (0–10 scale). Ratings are illustrative expert-elicitation estimates intended to visualize the qualitative trade-offs described in the text, not a systematic quantitative comparison drawn from the cited literature.*

4. Developmental and Regulatory Pathways

4.1 Orphan Drug Incentives

The US and EU have each established regulatory incentives for rare disease drug development. The US Orphan Drug Act of 1983 provides seven years of market exclusivity, clinical trial tax credits, and a waiver of FDA user fees; the EU Orphan Regulation of 1999 offers ten years of exclusivity, extendable to twelve years with completed pediatric studies (Jonker et al., 2023).

Despite these incentives, the number of FDA orphan-designated approvals rose only from 2 in 1983 to 33 by 2020—modest progress relative to the scale of unmet need. Some observers have also raised concerns that companies exploit orphan provisions for mainstream drugs rather than genuine rare disease needs (Kumar, 2025).

4.2 Regulatory Challenges Specific to Repurposed Drugs

Repurposed drugs face several distinct regulatory hurdles. Generating robust evidence from small patient samples remains, in the words of Cortial et al. (2024), a methodological and logistical challenge. Demonstrating superiority over existing treatment is often difficult given the constraints imposed by disease rarity. Data protection for repurposed medicines is proposed at four years where an unmet medical need and significant clinical benefit are demonstrated. And a lack of alignment—

and poorly timed interaction—between healthcare professionals and regulators creates additional friction (European Medicines Agency, 2022).

The European Medicines Agency's repurposing pilot found that academic teams typically required six months or more to prepare for Scientific Advice, and that most marketing authorization holders showed limited interest in pursuing new rare disease indications (European Medicines Agency, 2022).

4.3 Intellectual Property and Commercial Considerations

Intellectual property considerations shape the repurposing landscape substantially. An analysis of rare disease repurposing patents filed between 2010 and 2023 identified 190 such patents, 75% of which originated from small or medium-sized pharmaceutical companies or university spin-offs (Jonker et al., 2024).

This landscape remains complex: no dedicated patent category exists for repurposing content; patent protection for new uses of existing medicines plays a crucial role in creating viable development pathways; market exclusivity does not appear to be a primary motivator for nonprofit rare disease organizations; and excessive patent protection can, paradoxically, undermine successful repurposing (Kumar, 2025).

5. Case Studies in Rare Disease Drug Repositioning

5.1 Thalidomide

Thalidomide offers one of the most dramatic examples of drug repositioning in medical history. Marketed in the 1950s as a sedative and antiemetic for pregnant women, it caused severe birth defects and was withdrawn from the market.

Decades later, a physician in Jerusalem observed, through compassionate use, that thalidomide dramatically improved erythema nodosum leprosum (ENL), a rare complication of leprosy. Subsequent research showed that thalidomide acts by modulating immune response and inhibiting angiogenesis. The FDA approved thalidomide for ENL in 1998 and for multiple myeloma, a rare blood cancer, in 2006 (Kumar, 2025).

This case illustrates three recurring lessons: serendipitous clinical observation can yield major therapeutic breakthroughs; drugs with concerning safety profiles in one context may be used safely in another with appropriate risk management; and repositioning can convert a withdrawn or problematic drug into a valuable therapeutic tool.

5.2 Sildenafil

Sildenafil, originally developed for angina pectoris, was famously repurposed for erectile dysfunction and, subsequently, for pulmonary arterial hypertension (PAH), a rare and life-threatening condition.

More recently, sildenafil has shown promise in mitochondrial disease. Using iPSC-based drug discovery, researchers screened a compound library and identified sildenafil as a candidate for Leigh syndrome, a severe mitochondrial disorder. Chronic off-label, compassionate-use treatment of six patients showed good tolerability and clear clinical improvement; sildenafil has since received Orphan Drug Designation for Leigh syndrome and is now under evaluation in a pivotal Phase III trial (Hay Mele et al., 2024).

5.3 Sirolimus (Rapamycin)

Originally developed to prevent organ rejection after kidney transplantation, sirolimus has been repurposed for several rare genetic syndromes. By inhibiting the mTOR pathway, it reduces the abnormal cell growth that drives these disorders and has shown efficacy in congenital vascular malformations. A Radboudumc team won the Drug Repurposing Venture Challenge with a plan to make sirolimus formally available for this indication (Jonker et al., 2024).

5.4 An Unsuccessful Attempt: General Lessons from Failed Repurposing

Not all repurposing efforts succeed, and understanding failure is as instructive as celebrating success. Common causes include a lack of efficacy in the new indication despite encouraging preclinical data; unexpected toxicity when a drug is used in a different population or at a different dose; regulatory hurdles that cannot be resolved with available evidence; and commercial barriers that prevent investment in the clinical trials needed to confirm efficacy. Rituximab's evaluation for graft-versus-host disease, for example, was ultimately discontinued after toxicity concerns emerged (see Table 2).

As Kumar (2025) observes, although the number of novel rare disease treatments has grown substantially over recent decades, many conditions still lack an FDA-approved therapy; even scientifically promising candidates remain constrained by limited attention from for-profit pharmaceutical developers (Jonker et al., 2024).

Table 2. Illustrative case studies of drug repositioning in rare diseases.

Drug	Target Rare Disease	Original Use	Outcome	Year
Thalidomide	Multiple myeloma	Nausea in pregnancy	Approved (FDA)	1998/2006
Sildenafil	Pulmonary hypertension	Angina	Approved (FDA)	2005
Clozapine	Treatment-resistant schizophrenia*	Antipsychotic	Approved (restricted)	1989
Rituximab	Graft-versus-host disease	Cancer (lymphoma)	Discontinued (toxicity)	2008

** Not classified as a rare disease under standard prevalence criteria; retained here for methodological illustration and flagged for the authors to confirm inclusion criteria.*

5.5 Cross-Cutting Lessons

Four themes recur across successful and unsuccessful cases. Patient advocacy and collaboration are critical: nonprofit engagement, leveraging registries and direct outreach, has accelerated trial enrollment in several programs (Nijim et al., 2025). Early regulatory engagement matters: seeking scientific advice early and sharing clinical observations promptly smooths the development pathway (European Medicines Agency, 2022). Converging lines of evidence strengthen the case for repurposing, since computational prediction, experimental validation, and clinical observation are most persuasive in combination. And public–private collaboration accelerates progress, as innovation platforms, real-world data initiatives, and AI tools tend to be most effective when developed jointly across sectors (Jonker et al., 2023).

6. Challenges and Limitations Specific to Rare Diseases

6.1 Biological Uncertainties

Many rare diseases have poorly characterized pathophysiology, with unclear molecular pathways and an incomplete understanding of disease mechanisms. This uncertainty complicates both target selection and the interpretation of drug effects. Paquot et al. (2024) frame the core difficulty as one of insufficient accessible knowledge—about both the drug and the disease—needed to de-risk development in a new indication.

6.2 Small Patient Numbers and Trial Design Difficulties

Small, dispersed patient populations create substantial trial-design challenges: insufficient statistical power for conventional randomized trials, difficulty recruiting adequate samples, clinical heterogeneity that complicates outcome measurement, and a scarcity of validated outcome assessments. Cortial et al. (2024) summarize these as a combination of small, geographically dispersed populations, poorly developed endpoints, insufficient patient data, and inappropriate control groups.

6.3 Data and Evidence Gaps

Rare disease research is further constrained by fragmented patient data across institutions and countries, limited natural history data to inform trial design, an absence of validated biomarkers for many conditions, and publication bias toward positive results. Together, these gaps complicate both the identification of repurposing candidates and the generation of evidence sufficient for regulatory approval (Gangwal & Lavecchia, 2025).

6.4 Commercial and Financial Hurdles

Commercial barriers include limited financial incentive, given that companies often view rare disease repurposing as a suboptimal investment; payer reluctance to assign favorable prices to repurposed drugs; intellectual property challenges for off-patent compounds; and development

costs that are high relative to likely returns. Nijim et al. (2025) show that nonprofit engagement can offset some of these barriers by leveraging patient advocacy networks and registries to accelerate enrollment and improve the representativeness of study populations.

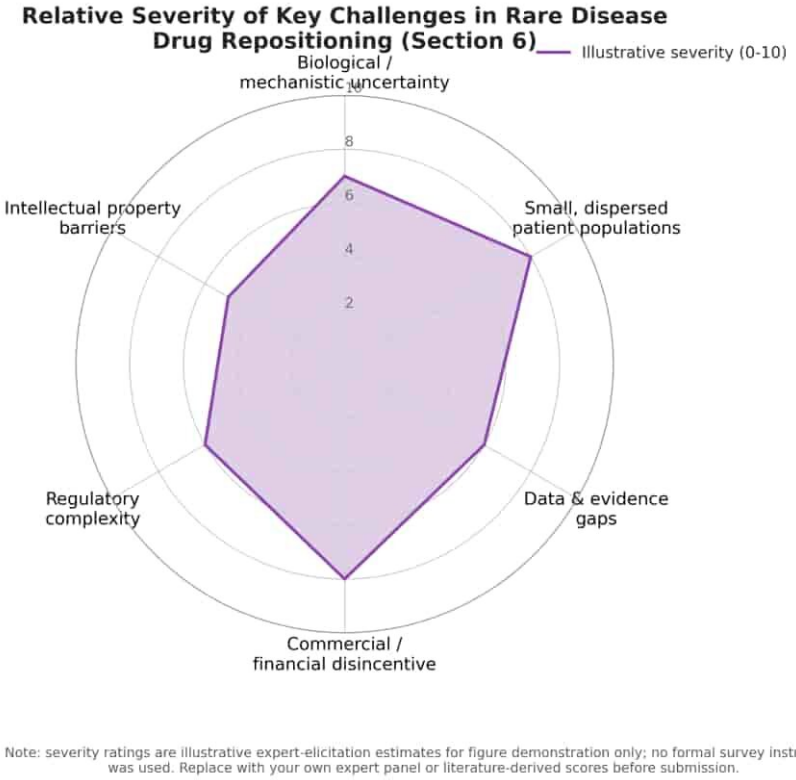

Figure 3. *Relative severity of the key challenges discussed in Section 6 (0–10 scale). Ratings are illustrative estimates for figure demonstration only; no formal expert-panel survey was conducted. Replace with literature-derived or panel-sourced scores before submission.*

6.5 Limitations of This Review

As a narrative rather than systematic review, this synthesis does not follow a pre-registered protocol, and source selection—while guided by the search strategy described in Section 3—was not exhaustive and may be subject to selection bias. The literature reviewed is predominantly in English and originates largely from North American and European sources, which may underrepresent repurposing initiatives elsewhere. Quantitative comparisons (cost and timeline estimates in Table 1) draw on a limited number of published estimates and should be interpreted as indicative rather than precise.

7. Future Perspectives and Opportunities

7.1 Precision Medicine and Patient Stratification

Advances in genomics and molecular biology increasingly allow precise characterization of rare diseases. Patient stratification—identifying subgroups most likely to respond to a given therapy—can improve the efficiency of repurposing efforts. Integrating multi-omics data (genomics, transcriptomics, proteomics, metabolomics) with clinical information supports more targeted repurposing; Gangwal and Lavecchia (2025) describe AI-driven advances in biomarker discovery as

central to overcoming the data limitations that have historically constrained rare disease drug discovery.

7.2 Real-World Evidence and Adaptive Trial Designs

Real-world evidence is an increasingly valuable complement to traditional trial data; platforms such as CURE ID collect real-world treatment data specifically to support repurposing in rare genetic disorders (Jonker et al., 2024). Adaptive designs, including basket trials that evaluate multiple rare disease indications within a single framework, can improve trial efficiency and relevance, accelerate patient access to candidate treatments, and support better-informed clinical decisions (Cortial et al., 2024).

7.3 Ethical and Economic Considerations

Several ethical and economic questions merit attention as repurposing efforts scale: ensuring access and affordability for patients who need repurposed drugs; addressing regional and population-level disparities in rare disease research and treatment; developing sustainable business models that do not rely on excessive pricing; and meaningfully engaging patients and families throughout the repurposing process. The IRDiRC Drug Repurposing Guidebook identifies patient engagement as a defining feature of successful repurposing initiatives (Jonker et al., 2023).

8. Conclusions

Drug repositioning offers a credible strategy for accelerating therapeutic development in rare diseases, reducing cost, time, and developmental risk relative to de novo discovery. The convergence of computational methods—network-based prediction, artificial intelligence, knowledge graphs—with experimental strategies such as phenotypic screening and patient-derived models is expanding what repurposing can achieve, while collaborative frameworks spanning academia, nonprofits, and industry are demonstrating that systematic repurposing is feasible even without traditional commercial incentives.

Progress nonetheless depends on addressing the structural barriers documented throughout this review: biological uncertainty, small and dispersed patient populations, persistent data gaps, and limited commercial interest. For the field to advance, three groups have distinct roles to play. Academic and clinical researchers should prioritize systematic documentation of off-label observations and early data sharing. Regulators should continue to clarify evidentiary pathways for repurposed indications, building on pilots such as the EMA's repurposing initiative. And industry and patient organizations should expand collaborative funding models that do not depend solely on patent-driven exclusivity. As the IRDiRC guidebook concludes, sharing clinical observations, engaging regulators early, and sustaining public–private collaboration remain the clearest path to bringing effective repurposed treatments to the millions of patients living with rare diseases (Jonker et al., 2023).

Declarations

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Authors' Contributions

KY: Conceptualization, investigation, data curation, and writing – original draft. **NS:** Methodology, validation, writing – review & editing, and project administration. **WG:** Resources, visualization, and writing – review & editing. All authors contributed to the final version and approved the manuscript for submission

Availability of Data and Materials

All data supporting the findings are included within the article and its tables. The full evidence table is available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

Consent for Publication

Not applicable.

Ethical Considerations

This study As a Narrative review of published studies, no primary data collection from human participants was conducted.

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Artificial Intelligence Disclosure

During the preparation of this narrative review, the authors used Python (version 3.x) with the Matplotlib library solely to generate the illustrative figures (Figures 1, 2, and 3). Additionally, the authors used Claude (Anthropic), a large language model, exclusively for language polishing, grammar correction, and clarity enhancement during the revision process. No artificial intelligence tools were used for data analysis, conceptualization, literature search, or the generation of scientific content. After using these tools, the authors carefully reviewed and edited the final manuscript and take full responsibility for the integrity, accuracy, and final content of this publication.

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Heshmati, H (2026).Reported Age at Marriage and Its Sociodemographic Correlates among Married Women in Torbat Heydarieh County, Northeastern Iran. *Health promotion sciences*, *2*(1), 47-55.

Reported Age at Marriage and Its Sociodemographic Correlates among Married Women in Torbat Heydarieh County, Northeastern Iran: A Cross-Sectional Study

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ABSTRACT. The timing of marriage is a critical demographic and life-course transition linked to family formation and reproductive trajectories. Its correlates vary significantly across different social and cultural settings. To describe the reported age at marriage and examine its unadjusted associations with educational level, occupational status, and number of children among married women in Torbat Heydarieh County, northeastern Iran.In this cross-sectional study conducted in 2026, 405 married women aged 15–49 years were recruited through multistage random sampling. Sociodemographic data was collected using a researcher-developed questionnaire, and the reported age at marriage was recorded via an open-ended question. Data were analyzed in IBM SPSS Statistics (Version 20) using descriptive statistics, one-way analysis of variance (ANOVA) with Fisher's LSD post hoc tests, and Pearson's correlation. No multivariable adjustment was performed. Valid data on the reported age at marriage were available for 391 participants (96.5%). The mean reported age at marriage was 21.93 years (SD=5.18; median = 21). It differed significantly by educational level (F=20.18,p<.001) and occupational status (F=10.22, p<.001). Women with a university education reported a higher mean age at marriage (23.36±4.29 years) compared to those with less than a high school education (19.47±4.67) or a diploma (20.78±6.09). Women employed outside the home reported a higher mean age at marriage than housewives (23.22±4.02 vs. 20.90±5.77years; p<.001). The mean also differed across categories of the number of children (F=13.75, p<.001), ranging from 24.39±4.24years among women with no children to 19.13±3.66among those with three or more. The reported age at marriage was negatively correlated with the number of children (r=-.301, p<.001; n=389). In this single-county sample, the reported age at marriage varied significantly across educational and occupational groups and was inversely correlated with the number of children. Given the cross-sectional design and the absence of multivariable adjustment, these findings describe unadjusted associations and do not imply causal relationships.

Keywords: age at marriage; women; education; employment; sociodemographic factors; Iran.

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1. Introduction

Marriage is a major life-course transition and a central component of family formation. Its timing matters for demographic change because it marks the formation of a union and, in many settings, the onset of childbearing. Marriage is a major life-course transition and a central component of family formation. Its timing is demographically significant as it often marks the formation of a union and, in many settings, the onset of childbearing.

Cross-national evidence indicates substantial variation in the timing of marriage across countries and regions, as well as shifts across birth cohorts. The United Nations World Marriage Data provides indicators of marital status and mean age at marriage for 232 countries, compiled from heterogeneous census and survey sources (United Nations, 2019).

Studies in developing countries have documented persistent, albeit declining, rates of early marriage, with marked regional disparities.

Analyses of Demographic and Health Surveys demonstrate that educational attainment is associated with the timing of marriage, although the magnitude and pattern of this association differ across settings (Jensen & Thornton, 2003; Singh & Samara, 1996). More recent comparative research indicates that educational expansion is accompanied by changes in marriage timing, particularly among women (Bongaarts et al., 2017; Wu & Pesando, 2025).

Iran has undergone substantial changes in marriage patterns, though these shifts have not been uniform across cohorts, regions, or social groups. Studies based on Iranian demographic and census data have documented marriage postponement, spatial and ethnic differences in the transition to first marriage, and the critical role of women's education and the broader socioeconomic context (Mahdaviazad et al., 2019; Torabi & Baschieri, 2010; Torabi et al., 2013).

Education may be linked to later marriage through several pathways, including prolonged participation in schooling, shifting role priorities, and changing expectations about family formation. For instance, a study based on Iran's Urban Time Use Survey suggested that education shapes women's transition to marriage through time allocation and the prioritization of roles beyond marriage (Torabi & Abbasi-Shavazi, 2016). Evidence from other settings, including Turkey and South Asia, similarly links higher educational attainment to later first marriage, though this relationship remains context-dependent (Caldwell, 2005; Bongaarts et al., 2017).

The association between employment and the timing of marriage is less straightforward. Employment measured at the time of a survey may not reflect a woman's labor-force participation prior to marriage, and marriage itself may subsequently affect employment. Cross-national evidence suggests that current employment differences by age at marriage can be weak in some settings, underscoring the need to avoid causal interpretations when the temporal order is unknown (Blossfeld, 2009). Furthermore, economic conditions and marriage-market institutions may shape the timing of marriage in context-specific ways (Corno et al., 2020).

The timing of marriage is also intrinsically related to reproductive trajectories. Later marriage may coincide with later entry into parenthood where childbearing is closely tied to marriage; however, the relationship with completed parity is not necessarily linear and may depend on fertility preferences, age, union duration, and social context (Compernolle & Axinn, 2019; Nitsche & Hayford, 2020). While research on child marriage has documented associations with educational disadvantage and early childbearing, findings on child marriage should not be conflated with the full distribution of ages at marriage among adult women (Arthur et al., 2018; Malhotra & Elnakib, 2021; Parsons et al., 2015; Plesons et al., 2021).

Although national and provincial studies have examined the timing of marriage in Iran, local evidence remains valuable because social and demographic patterns can vary across geographical settings. Measurement also matters: a reported age at marriage cannot be interpreted as the age at first marriage unless the questionnaire explicitly establishes that distinction.

This study, therefore, describes the reported age at marriage without reclassifying it as the age at first marriage, and examines its unadjusted associations with educational level, occupational status, and number of children among married women aged 15–49 years in Torbat Heydarieh County, northeastern Iran.

2. Methods

2.1. Study Design and Setting

This cross-sectional study was conducted in 2026 among married women aged 15–49 years residing in Torbat Heydarieh County, northeastern Iran.

2.2. Participants and Sampling

A total of 405 women were recruited through multistage random sampling. In the first stage, five comprehensive health centers were selected via simple random sampling. In the second stage, the sample was allocated to these centers using stratified sampling. In the third stage, participants

within each center were selected by simple random sampling. Eligible women were married, aged 15–49 years, willing to participate, without a history of mental illness, not taking antidepressant medication, and in adequate mental health to complete the questionnaire. Questionnaires with incomplete responses were excluded only from the specific analyses requiring the missing information.

2.3. Measures

Data were collected using a researcher-developed questionnaire. The sociodemographic section covered the reported age at marriage, educational level, and occupational status.

The reported age at marriage was recorded through an open-ended question. Because the questionnaire did not distinguish between the age at first marriage and the age at the current marriage, this variable is consistently referred to as the "reported age at marriage" throughout the manuscript.

Educational level was categorized as less than high school, diploma, or university. Occupational status, recorded at the time of the survey, was classified as housewife, employed outside the home, or home-based self-employed. The number of children was recorded via an open-ended question and categorized as 0, 1, 2, or 3 or more.

Content validity of the questionnaire was assessed by a panel of public health experts; however, formal reliability testing (Cronbach's alpha) was not conducted, which is acknowledged as a methodological limitation.

2.4. Statistical Analysis

Data were analyzed using IBM SPSS Statistics (Version 20). Descriptive statistics summarized the study variables.

One-way ANOVA was used to compare the mean reported age at marriage across educational, occupational, and number-of-children categories. Fisher's LSD post hoc comparisons were performed following statistically significant overall ANOVA results. Pearson's correlation coefficient was used to examine the relationship between the reported age at marriage and the number of children. The significance level was set at $p <$,05. Each analysis utilized available observations, resulting in varying sample sizes due to missing data. No multivariable analysis was performed; all reported associations are unadjusted.

2.5. Ethical Considerations

Participation was voluntary, and the questionnaires were anonymous. Informed consent was obtained from all participants prior to data collection, and confidentiality was strictly maintained. The study was approved by the Ethics Committee of Torbat Heydariyeh University of Medical Sciences (Ethics Code: IR.THUMS.REC.1403.014).

3. Results

3.1. Distribution of Reported Age at Marriage

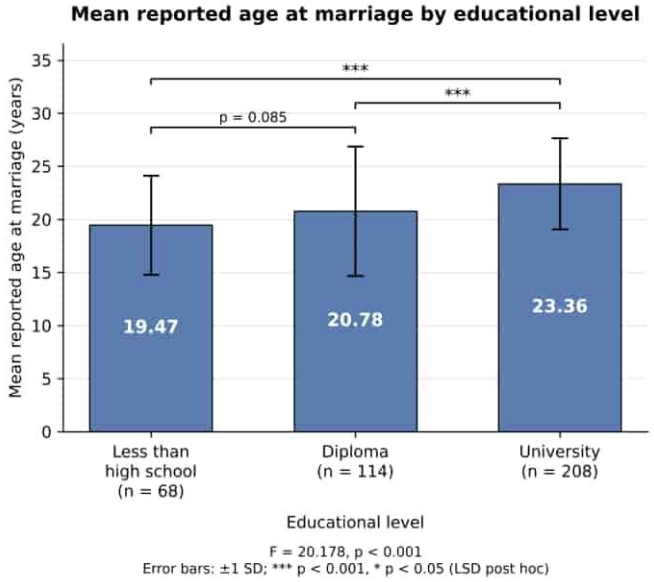
Of the 405 participants, 391 (96.5%) provided valid data on the reported age at marriage, while 14 (3.5%) had missing data. The mean reported age at marriage was 21.93 years (SD = 5,18), and both the median and mode were 21 years (Table 1). The minimum reported value of 10 years is addressed in Section 4.4.

Table 1. Distributional characteristics of the reported age at marriage among married women in Torbat Heydarieh County (N=405)

Statistic	Value
Total sample	405
Valid observations, *n*(%)	391 (96.5%)
Missing observations, *n*(%)	14 (3.5%)
Mean, years	21.93
Standard deviation, years	5.18
Median, years	21
Mode, years	21

3.2. Reported Age at Marriage by Educational Level

The mean reported age at marriage differed significantly across educational groups ($F = 20{,}18. p <$,001). It was $19{,}47 \pm 4{,}67$years among women with less than a high school education, $20{,}78 \pm$ 6,09among those with a diploma, and $23{,}36 \pm 4{,}29$among those with a university education. LSD post hoc comparisons revealed that the university group differed significantly from both lower-education groups (both $p <$,001), whereas the difference between the less-than-high-school and diploma groups was not statistically significant ($p =$,085) (Table 2, Figure 1).

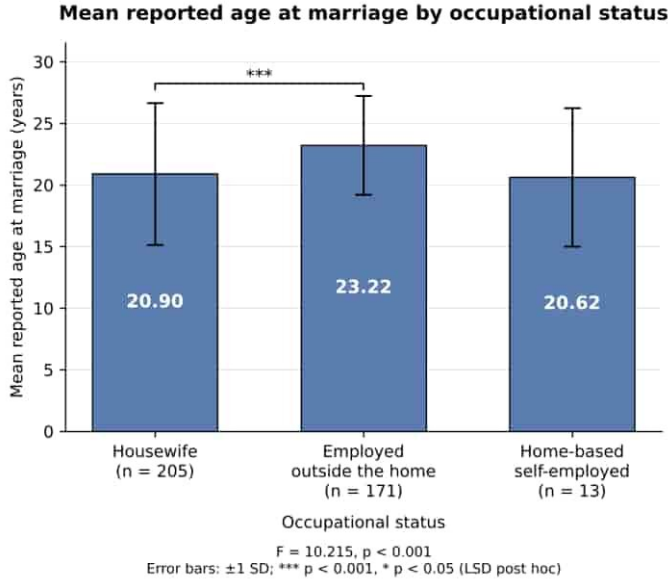


Note:*** p < 0.001 (LSD post hoc); the difference between less than high school and diploma was not significant (p = 0.085) Bars show means and error bars show ±1 SD (Table 2).

Figure 1. Mean reported age at marriage by educational level

3.3. Reported Age at Marriage by Occupational Status

The mean reported age at marriage differed significantly across occupational groups ($F = 10{,}22. p <$,001). Women employed outside the home reported a higher mean age at marriage ($23{,}22 \pm 4{,}02$ years) than housewives ($20{,}90 \pm 5{,}77$ years; $p <$,001). The mean among home-based self-employed women was $20{,}62 \pm 5{,}62$years. Other pairwise comparisons between occupational groups were not statistically significant (Table 2, Figure 2).



Note: Bars show means and error bars show ±1 SD (Table 2). *** p < 0.001 (LSD post hoc); other pairwise comparisons were not significant.

Figure 2. Mean reported age at marriage by occupational status

3.4. Reported Age at Marriage by Number of Children

The mean reported age at marriage differed significantly across categories of the number of children ($F = 13{,}75. p < {,}001$). The mean was highest among women with no children ($24{,}39 \pm 4{,}24$ years) and lowest among women with three or more children ($19{,}13 \pm 3{,}66$ years). LSD comparisons were significant for 0 versus 1, 2, and 3 or more children; for 1 versus 3 or more; and for 2 versus 3 or more. The difference between 1 and 2 children was not significant ($p = {,}106$) (Table 2, Figure 3).

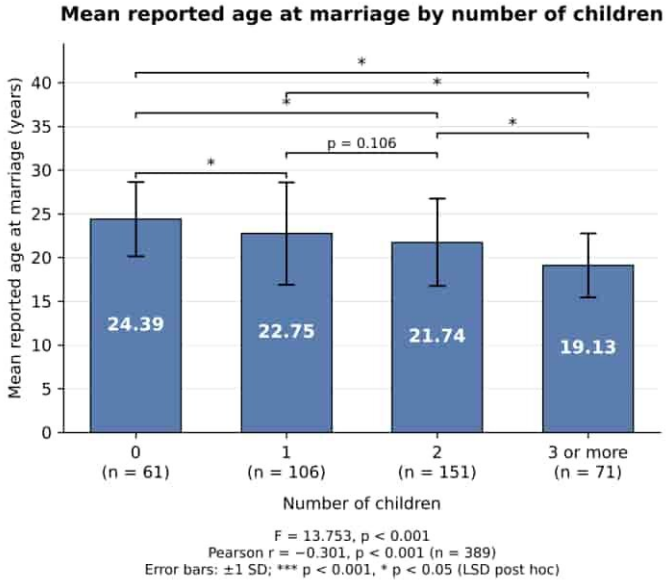
Table 2. One-way analysis of variance comparing the mean reported age at marriage across sociodemographic groups.

Characteristic	Category	n	Mean ± SD (years)	ANOVA
Education	Less than high school	68	19.47 ± 4.67	F = 20.178, p < 0.001
	Diploma	114	20.78 ± 6.09	
	University	208	23.36 ± 4.29	
Occupation	Housewife	205	20.90 ± 5.77	F = 10.215, p < 0.001
	Employed outside the home	171	23.22 ± 4.02	
	Home-based self-employed	13	20.62 ± 5.62	
Number of children	0	61	24.39 ± 4.24	F = 13.753, p < 0.001
	1	106	22.75 ± 5.87	
	2	151	21.74 ± 5.00	
	3 or more	71	19.13 ± 3.66	

ANOVA, one-way analysis of variance; SD, standard deviation. Group sizes differ between analyses because of missing data. LSD post hoc results are given in the text.

3.5. Correlation between the reported age at marriage and the number of children

Pearson's correlation showed a statistically significant negative association between the reported age at marriage and the number of children (r = −0.301, p < 0.001; n = 389) (Table 3).



Note: Bars show means and error bars show ±1 SD (Table 2). * p < 0.05 (LSD post hoc); the difference between 1 and 2 children was not significant (p = 0.106). Pearson's correlation between the reported age at marriage and the number of children: r = −0.301, p < 0.001 (n = 389).

Figure 3. Mean reported age at marriage by number of children

3.6. Correlation Between the Reported Age at Marriage and the Number of Children

Pearson's correlation revealed a statistically significant negative association between the reported age at marriage and the number of children ($r = -{,}301. p < {,}001; n = 389$) (Table 3).

Table 3. Pearson's correlation between the reported age at marriage and the number of children among women with complete data.

Variables	n	Pearson r	p-value
Reported age at marriage and number of children	389	−0.301	< 0.001

4. Discussion

This study examined the reported age at marriage and its unadjusted associations with educational level, occupational status, and number of children among married women in Torbat Heydarieh County. The mean reported age at marriage was 21.93 years. Significant differences were observed across educational and occupational groups, alongside a negative association with the number of children. All findings represent unadjusted, cross-sectional associations.

Women with a university education reported a higher mean age at marriage than women with lower educational attainment. This pattern aligns with Iranian studies documenting later first marriage among highly educated women and research linking educational expansion to marriage postponement (Mahdaviazad et al., 2019; Torabi & Baschieri, 2010; Torabi et al., 2013). Torabi and Abbasi-Shavazi (2016) suggested that education may influence marriage timing partly through time allocation and shifting role priorities, a pathway highly relevant to the Iranian context. International comparative studies similarly show that higher educational attainment is often associated with later marriage, though the magnitude of this association varies globally (Bongaarts et al., 2017; Caldwell, 2005; Wu & Pesando, 2025). In the present data, the primary difference lay between university-educated women and the other two groups, as the less-than-high-school and diploma groups did not differ significantly. Because the analysis was unadjusted and cross-sectional, these educational differences should be interpreted as group comparisons rather than evidence of a causal effect. Education may have been completed before or after the reported marriage, and the questionnaire did not establish this temporal sequence.

Women employed outside the home at the time of the survey reported a higher mean age at marriage than housewives. This finding may reflect differences in educational pathways, socioeconomic circumstances, or life-course priorities. However, occupational status was measured at the survey date, not necessarily at the time of marriage. Marriage may also influence subsequent employment, and international evidence suggests that the association between current employment and age at marriage is not uniformly strong across settings (Blossfeld, 2009). Therefore, reverse causation and confounding cannot be ruled out. Additionally, the small sample size of the home-based self-employed group limits the statistical power of comparisons involving this category.

The reported age at marriage was negatively correlated with the number of children, with the mean being lower among women with three or more children compared to those with none. A plausible explanation is that earlier marriage allows for a longer reproductive window in which childbearing can occur; however, the present data cannot test this hypothesis. Studies in other populations have linked marriage timing to entry into parenthood and achieved fertility, though these relationships are mediated by social norms, fertility preferences, age, and whether childbearing occurs primarily within marriage (Compernolle & Axinn, 2019; Nitsche & Hayford, 2020).

This correlation must not be interpreted as a causal effect of marriage age on family size. Current age, birth cohort, duration of marriage, fertility intentions, contraceptive use, infertility, socioeconomic conditions, and marital history may all influence the number of children, and none of these confounders were controlled in this analysis.

The minimum reported age at marriage was 10 years. Such a value may represent a genuine report, a misunderstanding of the question, or a data-entry error. Like any value below 18 years, it must be

interpreted with extreme caution. Research on child marriage in Iran indicates that early marriage varies by gender, ethnicity, parental literacy, and place of residence (Torabi & Bagi, 2024). While international reviews describe associations between child marriage and educational disadvantage or early childbearing, these findings pertain to a specific subgroup and should not be generalized to the entire present sample (Arthur et al., 2018; Malhotra & Elnakib, 2021; Parsons et al., 2015; Plesons et al., 2021).

Strengths and Limitations

The strengths of this study include recruitment through five comprehensive health centers using multistage random sampling and the examination of the reported age at marriage in relation to several key sociodemographic characteristics.

However, several limitations must be acknowledged. First, the cross-sectional design precludes temporal and causal inference. Second, the study was restricted to one county and recruited women through health centers, limiting generalizability to broader populations. Third, no multivariable adjustment was performed, meaning residual confounding (e.g., by current age or socioeconomic status) is highly likely. Fourth, occupational status was measured at the survey date, not at the time of marriage. Fifth, the questionnaire did not distinguish between the age at first marriage and the age at the current marriage, limiting direct comparison with studies that explicitly measured first marriage. Sixth, the reported age at marriage was self-reported and subject to recall bias; the minimum reported value of 10 years requires verification against source records. Finally, missing observations resulted in varying sample sizes across analyses, and one occupational group was notably small. Furthermore, formal reliability testing of the researcher-developed questionnaire was not conducted, which is a methodological constraint.

5. Conclusion

Among married women aged 15–49 years in Torbat Heydarieh County, the reported age at marriage differed significantly by educational level and occupational status and was negatively correlated with the number of children. These unadjusted, cross-sectional findings indicate that the reported age at marriage varies across sociodemographic groups in this local population, but they do not establish causal relationships. Future studies should employ an explicitly defined measure of age at first marriage, collect comprehensive socioeconomic and life-course data, ensure instrument reliability, and apply multivariable analyses to control for confounding factors.

Declarations

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The author sincerely thanks all participants for their valuable contributions to this Data Authors' **contributions**

The author contributed to all stages of the research and the preparation of the manuscript. study.

Availability of Data and Materials

Datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The author declares no conflicts of interest.

Consent for Publication

Not applicable.

Ethics approval and consent to participate

Ethical approval was granted by the Ethics Committee of Torbat Heydariyeh University of Medical Sciences (Code: IR.THUMS.REC.1403.014). Informed consent was obtained from all participants.

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Declaration of AI Use

Python was used for figure generation, and AI tools were utilized for language editing and formatting refinement in this paper.

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Benchmarking Switzerland's Health System Against the WHO Building Blocks: A Policy-Focused Systematic Review (2020–2025)

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ABSTRACT. Switzerland combines universal mandatory health insurance with some of the highest health expenditure in the OECD, within a federal structure in which the cantons play a central role. The COVID-19 pandemic exposed tensions between efficiency and resilience in this model. The WHO health-system building-blocks framework offers a multidimensional basis for assessing such performance. To benchmark the performance of the Swiss health system against the EU-15 average for 2020–2025 using the six WHO building blocks, and to identify strengths, persistent gaps and policy priorities, with particular attention to intensive care capacity and resilience. A policy-focused systematic review was conducted following PRISMA 2020. PubMed, Scopus and Web of Science were searched for publications from 2020 to 2025 (English, German, French) and complemented by official sources (Federal Office of Public Health, Federal Statistical Office, OECD, WHO Global Health Observatory). Quantitative indicators were extracted into a matrix aligned with the building blocks and compared with the EU-15 average; policy documents and grey literature were synthesised thematically. Study quality was appraised with design-appropriate tools (JBI, MMAT, AXIS, CASP). Of 1,247 records identified, 52 sources were included. Switzerland exceeded the EU-15 average for life expectancy at birth (84.0 vs 82.1 years), practising physicians (4.4 vs 4.0 per 1,000), nursing professionals (17.6 vs 9.5 per 1,000) and MRI units (34.2 vs 19.0 per million population). Health expenditure per capita was about 1.9 times the EU-15 average (USD PPP 9,351 vs 4,888; 11.6% vs 10.2% of GDP), and out-of-pocket payments accounted for a larger share of total expenditure (23.4% vs 15.1%). Intensive care capacity before the pandemic was below the EU-15 average (8.9 vs 11.5 beds per 100,000 population). An education-related life-expectancy gap of about 5 years (about 4 years in the EU-15) and geographical inequalities in health indicators were identified. Switzerland performs strongly on health outcomes, technological resources and workforce density, but it's very high expenditure is accompanied by only modest outcome advantages, a considerable financial burden on households, limited surge capacity and uneven cantonal coordination. Priorities are value-based financing, resilience planning decoupled from occupancy-based payment, stronger federal–cantonal coordination, and integration of primary care and digital health. The findings are relevant for other federal health systems.

Keywords: Switzerland; health system performance; WHO building blocks; health policy; universal health coverage; health system resilience

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1. Introduction

The Swiss health system is a federally organised model built on mandatory health insurance and regulated competition among private insurers. Insurance has been compulsory for all residents since 1996, and the cantons carry major responsibilities for planning and financing hospital care and for ensuring outpatient and long-term care (De Pietro et al., 2015). The system is consistently associated with excellent health outcomes, yet its per-capita cost is among the highest in the world (OECD, 2025), which raises questions about value for money and sustainability.

The period from 2020 to 2025, framed by the COVID-19 pandemic and its aftermath, represents a stress test of the system's resilience. Rankings based on outcomes alone do not show where in the system strengths and weaknesses arise, nor how they relate to financing, workforce, governance and surge capacity.

The WHO health-system building-blocks framework describes six components – service delivery, health workforce, health information systems, access to essential medicines, financing, and leadership/governance – that together contribute to the overarching goals of improved health, responsiveness, financial protection and efficiency (World Health Organization [WHO], 2010). This article uses the framework to move beyond outcome-based rankings and to provide a diagnostic, multi-layered analysis of the Swiss system against international peers.

The aim of this review is to benchmark the performance of the Swiss health system against global and European standards for 2020–2025 using the WHO building blocks, and to identify systemic strengths, persistent gaps and strategic priorities for policy reform, with a particular focus on intensive care capacity and resilience. Three questions guided the review: (1) How does Switzerland perform on quantitative indicators for each building block relative to the EU-15 average? (2) What does the policy and governance evidence say about the reasons for observed strengths and gaps? (3) Which reforms are indicated, and for which stakeholders?

2. Methods

2.1 Design and reporting

A policy-focused systematic review was conducted and is reported according to the PRISMA 2020 statement (Page et al., 2021). Unlike a classical systematic review that aggregates clinical evidence, this design integrates several forms of evidence – peer-reviewed studies, quantitative system indicators, policy evaluations and governance analyses – to inform high-level policy decisions. Two evidence streams were used: (i) a systematic search of bibliographic databases, documented in the left branch of the PRISMA flow diagram (Figure 1); and (ii) targeted retrieval of indicators and policy documents from official sources, documented in the "other methods" branch. The review protocol was not formally registered in a public repository.

2.2 Analytical framework

The review protocol was structured around the six WHO building blocks. Key questions were formulated for each block (for example, "How equitable and efficient is the financing system?"). Table 1 shows how each component of the framework was operationalised. The overall goals of the framework (health outcomes and equity) were treated as outcome dimensions rather than as building blocks. For health information systems and leadership/governance, no quantitative indicator was extracted; these blocks were analysed qualitatively.

Table 1. Operationalization of the WHO framework in this review

Framework component	Quantitative indicators (Table 3)	Qualitative evidence examined
Overall goals: health outcomes and equity	Life expectancy at birth; potential years of life lost; life-expectancy gap by education	Inter-cantonal disparities in health indicators
Service delivery (including physical resources)	Hospital beds; ICU beds; MRI units	Surge capacity; hospital payment; primary care
Health workforce	Practising physicians; nursing professionals (per 1,000)	Shortages; geographic distribution
Health information systems	None extracted	Cantonal information systems; integration
Access to essential medicines	Pharmaceutical expenditure per capita	Cost drivers
Financing	Total health expenditure per capita and % of GDP; out-of-pocket share	Payment mechanisms; premiums; transfers
Leadership and governance	None extracted	Federal–cantonal coordination; crisis governance

2.3 Eligibility criteria

Studies and documents were selected according to the criteria in Table 2.

Table 2. Inclusion and exclusion criteria

Criterion	Inclusion	Exclusion
Time period	2020–2025	Published before 2020
Language	English, German, French	Other languages
Document type	Original research articles; policy documents; official government/organisational reports	Review articles, editorials, commentaries, conference abstracts, book chapters
Geographic scope	Switzerland (federal and cantonal level)	Studies conducted exclusively outside Switzerland
Target population	General population, vulnerable groups, policy-makers, healthcare professionals	Animal studies; theoretical models without empirical data
Full-text availability	Full text accessible	Abstract only or inaccessible full text

Note on review-type sources: Comprehensive health system reviews (e.g., Health Systems in Transition) were treated as official organisational reports and included, while standard academic review articles were excluded to prioritise primary empirical and policy data.

2.4 Information sources and search strategy

Systematic searches were conducted in PubMed, Scopus and Web of Science for publications from 2020 to 2025. Parallel retrieval was performed from official sources: the Swiss Federal Office of Public Health (FOPH), the Federal Statistical Office (FSO), the WHO Global Health Observatory and OECD health statistics. The exact date of the last search was not systematically recorded in the project files. Keywords for the searches included “Switzerland health system”, “health financing” and “health workforce”, combined with “benchmarking”, “performance” and “COVID-19 impact”. The PubMed search string was:

> ("Switzerland"[Mesh] OR "Swiss health system") AND ("health policy"[Mesh] OR "health reform" OR "healthcare system") AND ("2020/01/01"[Date - Publication] : "2025/12/31"[Date - Publication])

Filters: English, German, French; human studies; full text.

2.5 Study selection

Records were managed using reference management software (specific software not recorded in project files), and duplicates were removed. Two reviewers independently screened titles and abstracts and then full texts. Disagreements were resolved by consensus or by a third reviewer. Inter-rater agreement was assessed during the screening process to ensure consistency.

2.6 Data extraction and normalisation

Data were extracted with a pre-tested form capturing author(s), year, study design, sample characteristics, setting, key outcomes and policy implications. Quantitative indicators were extracted from OECD health statistics, the WHO Global Health Observatory and FSO reports, organised by building block, cleaned and normalised for cross-country comparison (population-based units, USD purchasing-power parity, percentage of GDP). The EU-15 average was the primary benchmark, using the latest available data (approximately 2022–2023). The EU-15 average was calculated as the simple arithmetic mean of the 15 countries.

2.7 Quality appraisal

The methodological quality of included studies was appraised with tools matched to study design: JBI critical appraisal checklists, the AXIS tool for cross-sectional studies, CASP checklists for qualitative studies and the MMAT for mixed-methods studies. Confidence in the thematic findings drawn from qualitative and policy evidence was assessed with GRADE-CERQual. Official reports and grey literature were appraised with the AACODS checklist.

2.8 Synthesis

Extracted data were categorised according to the six WHO building blocks. Quantitative indicators were compared descriptively with the EU-15 average; no statistical pooling was performed because indicator definitions and sources differ. Policy documents and legislative texts were analysed thematically to explain the quantitative patterns, and numerical

benchmarks were integrated narratively with qualitative insights on policy successes and failures.

3. Results

3.1 Study selection

The database search identified 1,247 records. After records were removed before screening (including duplicates), 856 records were screened by title and abstract, 214 reports were sought for full-text assessment, and 52 sources were included in the review (Figure 1).

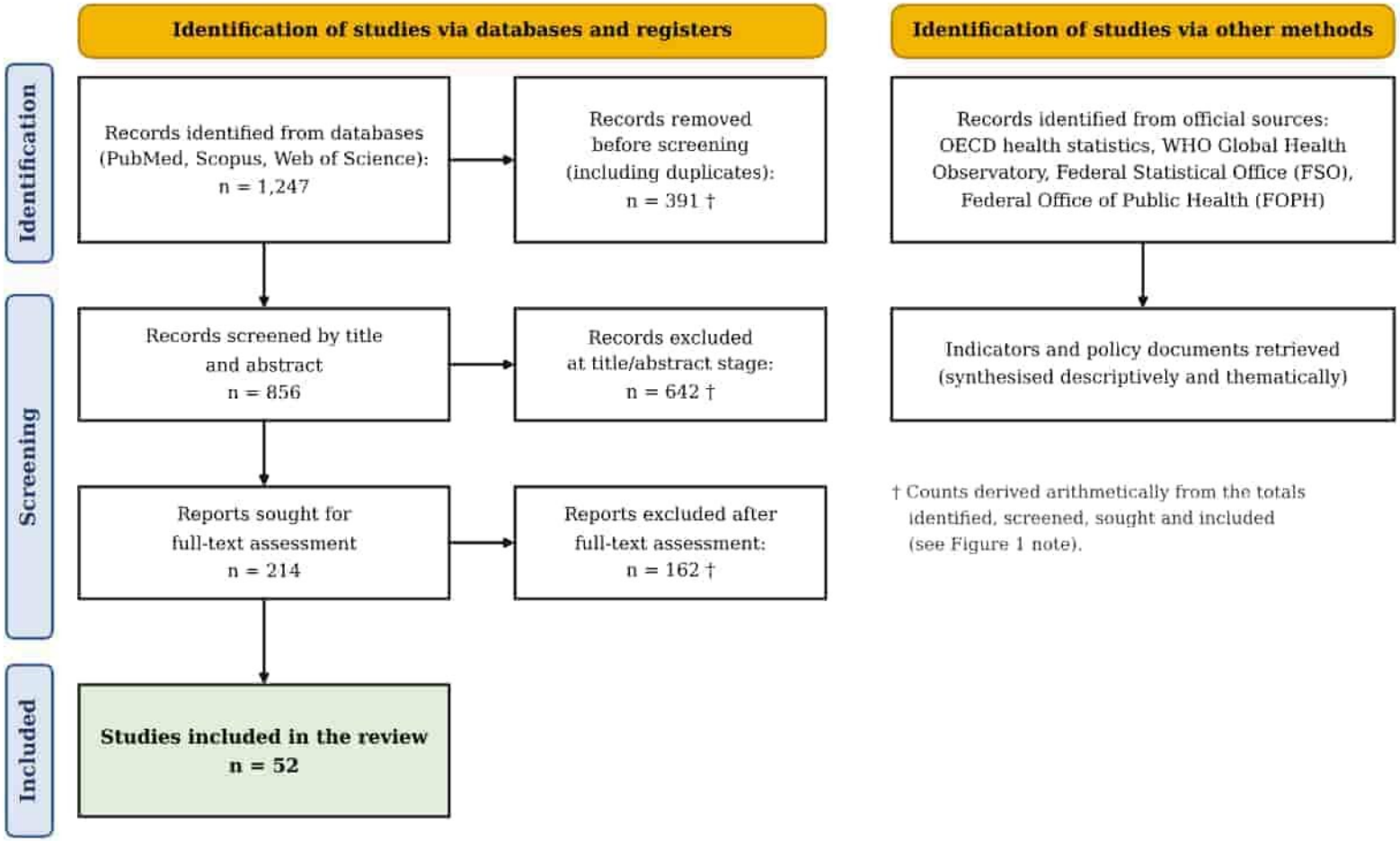

Figure 1. PRISMA 2020 flow diagram of study selection (adapted from Page et al., 2021; CC BY 4.0). *Where feasible, report the number of records identified from each database. **If automation tools were used, report how many records were excluded by humans and by automation. † The counts for records removed before screening (n = 391), records excluded at the title/abstract stage (n = 642), and reports excluded after full-text assessment (n = 162) are derived arithmetically from the total records identified (1,247), screened (856), sought for retrieval (214), and included (52). This derivation assumes that all 214 sought reports were successfully retrieved. Detailed, itemized reasons for exclusion and the exact screening log were not systematically recorded in a format that allows categorical breakdown, and thus are not presented here.

3.2 Core health-system indicators

Table 3 compares Switzerland with the EU-15 average on the core indicators, grouped by building block. Differences quoted in the text were calculated from the values in the table.

Table 3. Core health-system indicators: Switzerland versus the EU-15 average (latest available data, approximately 2022–2023)

WHO component	Indicator	Switzerland	EU-15 average	Note
Overall goals: outcomes	Life expectancy at birth (years)	84.0	82.1	Consistent strength
Overall goals: outcomes	Potential years of life lost per 100,000 population	3,200	4,100	Lower premature mortality
Overall goals: equity	Life-expectancy gap, low vs high education (years)	~5	~4	Significant inequity
Health workforce	Practising physicians per 1,000 population	4.4	4.0	Above average, but maldistribution
Health workforce	Nursing professionals per 1,000 population	17.6	9.5	High, but workload concerns
Financing	Total health expenditure per capita (USD PPP)	9,351	4,888	Among the highest in the OECD
Financing	Total health expenditure (% of GDP)	11.6	10.2	High economic footprint
Financing	Out-of-pocket payments (% of total health expenditure)	23.4	15.1	High burden on households
Service delivery	Hospital beds per 1,000 population	4.5	4.9	Slightly below average
Service delivery	ICU beds per 100,000 population (early 2020)	8.9	11.5	Critical gap identified
Service delivery	MRI units per million population	34.2	19.0	Excellent technical resources
Access to medicines	Pharmaceutical expenditure per capita (USD PPP)	1,102	756	Major cost driver

Sources: OECD Health Statistics 2024 (OECD, 2024); WHO Global Health Observatory (WHO, n.d.); Swiss FSO (Federal Statistical Office, 2023).

3.3 Findings by building block

Overall goals: outcomes and equity. Life expectancy at birth in Switzerland was 1.9 years higher than the EU-15 average (84.0 vs 82.1 years), and potential years of life lost were lower. Equity gaps were nevertheless apparent: the life-expectancy difference between people with low and high education was about 5 years in Switzerland compared with about 4 years in the EU-15. Furthermore, geographical inequalities in life expectancy indicators have been documented in Swiss research; for instance, in Geneva, clusters of earlier-than-expected mortality were significantly associated with lower neighbourhood income and socioeconomic gradients (Ladoy et al., 2021).

Service delivery. Hospital bed density was slightly below the EU-15 average (4.5 vs 4.9 per 1,000), and ICU capacity was about 23% lower (8.9 vs 11.5 beds per 100,000 population in early 2020). In contrast, technical equipment was abundant: 34.2 MRI units per million population, about 1.8 times the EU-15 average.

Health workforce. Aggregate densities were high: 4.4 practising physicians per 1,000 population (EU-15: 4.0) and 17.6 nursing professionals per 1,000 (EU-15: 9.5, a ratio of about 1.9). The included sources describe pronounced regional differences in the distribution of physicians and workload concerns among nurses.

Financing. Total health expenditure per capita was about 1.9 times the EU-15 average (USD PPP 9,351 vs 4,888) and represented 11.6% of GDP compared with 10.2%. Out-of-pocket payments accounted for 23.4% of total expenditure, 8.3 percentage points above the EU-15 average (15.1%).

Access to essential medicines. Pharmaceutical expenditure per capita was USD PPP 1,102 compared with 756 in the EU-15 (about 46% higher), identifying medicines as a major cost driver.

Health information systems and governance. The health information system was described as technologically advanced. Governance is characterised by federal decentralisation: the cantons plan and finance hospital care, and intensive care capacity was planned at cantonal level without a national strategic reserve(Table 4).

Table 4. Policy roadmap

Level	Recommendation	Primary stakeholder	Indicative timeline
Federal	Link federal health transfers to cantons to cost-efficiency conditions; shift policy focus from cost containment to value-based care, including population-based payment elements for chronic care	Federal Government	Short-term (1–2 years)
Federal	Mandate resilience planning: integrate capacity buffers (ICU, workforce) into national planning, finance them through dedicated resilience funds decoupled from daily occupancy, and set minimum national standards for resource distribution and crisis preparedness	FOPH, with cantonal health directors	Medium-term (2–4 years)
Cantonal	Integrate health information systems across cantons, including monitoring of ICU capacity	Cantonal governments	Medium-term (2–4 years)
Local	Expand primary care in underserved areas	Local health networks	Short-term (1–2 years)
Workforce	Strengthen recruitment, training and retention of nursing staff so that surge capacity can be staffed	FOPH, with cantons and hospitals	Medium-term (3–5 years)
Technology	Invest in telemedicine and digitally supported integrated care	Public–private partnership	Long-term (5+ years)

4. Discussion

Benchmarked against the EU-15 average, the Swiss health system combines clear strengths – life expectancy, workforce density and technological resources – with three main weaknesses: very high and household-intensive costs, equity and cantonal disparities, and limited surge capacity in intensive care. These patterns are discussed below in relation to the building blocks that explain them.

Swiss health expenditure is an outlier: spending per capita is about 1.9 times the EU-15 average, whereas the advantage in life expectancy is 1.9 years (84.0 vs 82.1). This suggests diminishing returns and potential inefficiencies in the financing and payment mechanisms, although outcome differences between countries cannot be attributed to health spending alone, since socioeconomic and lifestyle factors and lagged effects also play a role. Spending growth in Switzerland has been linked mainly to rising spending per patient rather than to population growth or ageing alone (Stucki et al., 2023). The high out-of-pocket share (23.4% vs 15.1%) indicates a substantial financial burden despite universal coverage, consistent with earlier assessments that lower- and middle-income households contribute a larger share of their income to financing the system (De Pietro et al., 2015).

National averages mask considerable variation. The Swiss system has been described as a federation of 26 cantonal systems with fragmented provision and financing, which produces geographical differences in expenditure (Marti et al., 2019). The geographical differences in life expectancy and the differences across education groups reported here point in the same direction. Decentralised governance preserves local responsiveness but makes it harder to set uniform minimum standards for the distribution of resources, for example for physicians and intensive care capacity.

The pandemic exposed a critical vulnerability in service delivery and resources: limited intensive care capacity. With 8.9 ICU beds per 100,000 population in early 2020, Switzerland was at the lower end of European preparedness.

Pre-pandemic baseline. The low baseline reflects long-term planning for efficiency and high occupancy, which left little buffer capacity. A system operating close to its capacity under normal conditions is, by definition, poorly equipped to absorb a surge. Pandemic stress test. During peak waves, capacity had to be scaled up quickly and elective care postponed, a strategy with deferred health costs. The crisis highlighted the trade-off between static efficiency and dynamic resilience.

Systemic roots. Three mechanisms are identified, Financing and incentives: the DRG-based hospital payment system (SwissDRG) rewards throughput and high occupancy and does not reward idle surge capacity, Governance and planning: decentralised, cantonal-level ICU planning without a national strategic reserve, Workforce: beds are of little use without staff; chronic nursing shortages made it difficult to staff additional beds at safe ratios.

Post-2020 reforms and remaining gaps. Temporary federal subsidies are reported to have raised capacity, but sustained funding is uncertain. Proposed reforms include building on the existing national ICU registry – the minimal dataset of the Swiss Society of Intensive Care Medicine, which covered all 84 certified ICUs in analyses of the first pandemic year (Previsdomini et al., 2024) – to support coordinated capacity planning, and revising financing to include resilience premiums. Without a shift from "just-in-time" to "just-in-case" planning, the fundamental vulnerability remains.

Lessons for other federal health systems, Federal–cantonal (or equivalent) coordination is essential in crises and needs a clear mandate, Strategic reserves of critical equipment and capacity buffers should be planned nationally., Investment in primary care can reduce pressure on hospitals, Insurance mandates must be balanced with affordability for households.

Strengths and limitations

Strengths of this review are the explicit use of an internationally recognised framework, reporting according to PRISMA 2020, and the combination of quantitative benchmarks with policy and governance evidence. Limitations are as follows. The search was restricted to English, German and French sources. Access to some cantonal data was incomplete. Publication bias may affect the grey literature. Official international data lag by two to three years, so developments in 2024–2025 are only partly captured. Attributing outcomes to specific system components is difficult in a multi-causal environment. Indicator definitions, reference years and data sources differ between indicators, and no weighting or statistical pooling was applied.

5. Conclusions

Benchmarking through the WHO framework reveals a Swiss health system with strong outcomes, information and technological resources, alongside very high costs, moderate inequities and fragile surge capacity. The path forward requires balancing the system's precision with the flexibility needed to withstand future shocks, in order to ensure sustainability, equity and resilience in 2025 and beyond. Table 4 translates the findings into recommendations by level of government and stakeholder. Recommendations for future research, Comparative analysis with Nordic health systems, Economic evaluation of the proposed reforms, Impact assessment of artificial intelligence on the efficiency of the Swiss health system.

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The authors declare no competing interests.

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Data availability

The full list of the 52 included sources, the data extraction matrix, and the PRISMA 2020 checklist are available from the corresponding author upon reasonable request.

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