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A Systematic Review of the Burden of Disease Studies on Diabetes

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ABSTRACT

Diabetes is a major cause of morbidity and premature mortality on a global scale, and its prevalence has been increasing in recent decades. The overall health impact of the disease is measured by disability-adjusted life years (DALYs), which is the sum of years of life lost due to disability (YLDs) and years of life lost due to premature death (YLLs). This systematic review was conducted to evaluate studies that estimated the burden of diabetes at the global, national, or regional level, and to identify and review the epidemiological metrics (DALYs, YLDs, YLLs, incidence, prevalence, and mortality) and the methods used to determine the burden of disease. A comprehensive search strategy was employed to identify eligible studies published between January 1, 2000, and December 31, 2024, in MEDLINE, Scopus, ScienceDirect, BioMed Central and CINAHL databases. The study was conducted in accordance with the PRISMA 2020 guidelines. Studies that utilized DALYs or their subsets (YLDs/YLLs) as measures of the health impact of diabetes and that were published in English were included in the review. Following a thorough evaluation of the relevant literature, a total of 16 studies out of 1,307 were deemed to be eligible for review. This research reveals a lack of harmonization of epidemiological data and methods that hinder the capacity for meaningful comparisons across studies of the burden of diabetes. The findings

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outlined in this study provide a comprehensive framework for the diversification of diabetes burden of disease studies across different countries and regions, with a particular focus on the global level.
Keywords: Diabetes Mellitus, Disability-Adjusted Life Years, Global Burden of Disease, Systematic Review

INTRODUCTION

Diabetes is among the foremost causes of death and disability on a global scale, affecting individuals irrespective of their geographical location, gender, or age group. The prevalence of diabetes is increasing at a consistent rate, representing a substantial threat to public health. Concurrently, diabetes was designated as one of the five priority non-communicable diseases targeted in the 2011 Political Declaration on the Prevention and Control of Non-Communicable Diseases. In 2021, it was estimated that approximately 537 million people worldwide had diabetes. The 10th edition of the International Diabetes Federation Atlas corroborates the notion that diabetes is an epidemic and one of the fastest-growing global health emergencies of the twenty-first century, with projections of 1.3 billion cases by 2050 (Abbafati et al., 2024; Armocida et al., 2024). These figures underscore the pressing need to address the escalating prevalence of diabetes. Lifestyle diseases, including diabetes, are undoubtedly a growing problem of our time, both locally and globally (Kotwas et al., 2021).

The Global Burden of Disease Study (GBD) uses four main indicators to calculate the burden of disease: mortality, life years lost due to premature death (YLLs), life years lived with disability (YLDs), and disability-adjusted life years (DALYs), which is the sum of the last two (Duncan et al., 2020). DALYs were first introduced by Murray in 1994 (Oliveira et al., 2024). DALY is a population health metric that measures the disease burden of a population by combining mortality in YLL and morbidity in YLD. This important global effort utilizes a health metric to estimate fatal and non-fatal health outcomes, allowing the impact of different diseases, injuries, and risk factors to be compared over time and across geographies. Consequently, the DALY concept offers a holistic perspective on health and serves as a valuable tool for informing decisions on disease prevention (Charalampous et al., 2022).

Studies estimating DALYs for diabetes have the capacity to provide insight into the epidemiological data sources and methodological approaches used to assess the

burden of the disease. The primary objective of this systematic review is to provide a comprehensive overview of studies that estimate the burden of diabetes using DALY, YLD, and YLL metrics. Secondary objectives include the identification of epidemiological measures (e.g. incidence, prevalence, mortality) and the evaluation of methodological approaches employed across global, national, and regional studies.

METHODOLOGY

The present study was conducted by searching online databases in December 2024, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

Search Strategy and Data Sources

The objective of this systematic review was to identify research articles that focused on the disease burden of diabetes. A comprehensive search strategy was employed across five databases (i.e., MEDLINE, Scopus, ScienceDirect, BioMed Central, and CINAHL) to identify diabetes disease burden studies published between 1 January 2000 and 31 December 2024. The search terms and numbers utilized are delineated in Table 1.

Table 1: Search terms used in databases

Database	Search Terms	Number of Articles
MEDLINE	(Disability-Adjusted Life Years OR (DALY OR DALYs) OR YLL OR YLLs AND (MH "Diabetes mellitus diseases OR diabetes type 1 diabetes OR type 2 diabetes"))	404
Scopus	(TITLE-ABS-KEY("disability-adjusted life year") OR TITLE-ABS-KEY("years of life lost") OR TITLE-ABS-KEY(daly OR dalys OR (disabil*) near/4 (adjust*) near/4 (life*) near/4 (year*)) OR TITLE-ABS-KEY(yll) OR TITLE-ABS-KEY(ylls) OR TITLE-ABS-KEY((year*) next/2 (life*) next/1 (lost*)) OR TITLE-ABS-KEY(yld OR ylds) OR TITLE-ABS-KEY((year*) near/3 (lived) near/3 (disabil*)) AND TITLE-ABS-KEY(("diabetes mellitus" OR "diabetes" OR "diabet" OR "Type 1 diabetes" OR "Type 2 diabetes"))) AND PUBYEAR > 1999 AND PUBYEAR < 2025 AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (DOCTYPE,"ar"))	721
ScienceDirect	"Disability-adjusted life years" OR "DALY" OR "DALYs" AND ("diabetes mellitus" OR "diabetes" OR "type 1 diabetes OR type 2 diabetes"))	162
BioMed Central	TI "Disability-Adjusted Life Years" OR TI "DALY" AND TI "Diabetes Mellitus" OR "Type 1 Diabetes OR Type 2 Diabetes"	14
CINAHL	TI "Disability-Adjusted Life Years" OR "DALY" AND TI ("Diabetes Mellitus" OR "Type 1 diabetes OR Type 2 diabetes")	6

The Mendeley Reference Manager (2.77.0) tool was utilized to organize the data, avoid duplication, and identify studies containing relevant keywords. A total of 1,307 studies satisfied the predetermined eligibility criteria and were incorporated into the search strategy. Concurrently, research sources were methodically categorized according to their respective subjects and significance.

Eligibility Criteria

This systematic literature review included studies that assessed the disease burden of diabetes using YLD and YLL as defined in the DALY and/or DALY framework. The review was restricted to studies that directly assessed the disease burden of diabetes. It is important to note that studies assessing the burden of diseases associated with risk factors of diabetes were excluded from the analysis. This is due to the fact that the definition of diabetes varies over time and geography. Moreover, conference abstracts, proceedings, editorials, and letters were excluded from the study. Despite the absence of geographical limitations in the study, the inclusion criteria were confined to research articles published in English. The inclusion and exclusion criteria are presented in Table 2.

Table 2: Inclusion and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
Studies using DALYs metrics	Studies not using DALYs measures Studies assessing the burden of disease related to risk factors of diabetes
Full-text research articles	Publications other than full-text research articles • Conference abstracts, • Proceedings paper, • Letters, • Editorials
Full-text research articles published between January 1, 2000-December 31, 2024	Studies published before January 1, 2000 and after December 31, 2024
Studies published in English language	Non-English language publications

Data Extraction

The present study incorporated research papers that adopted a burden of disease approach and evaluated DALYs for diabetes. The selection of studies and extraction of data were conducted by one researcher, with the validation of data elements performed by a second researcher. All studies from the databases that were included in the analysis were transferred to Mendeley (2.77.0). A thorough review of all transferred articles was conducted by two independent reviewers. The resolution of disagreements pertaining to inclusion and exclusion was attempted through the utilisation of a consensus-driven approach amongst the reviewers. A preliminary evaluation of the relevant studies was conducted on the basis of title and abstract, after which a selection was made for further analysis of the full texts. These were then subjected to a rigorous review by analysts, who were tasked with determining their conformity with the aforementioned selection criteria. Following the initial eligibility process, the studies were subjected to a more thorough investigation through a full-text review. Those that failed to satisfy the predetermined criteria were subsequently excluded from the analysis.

The study data were then subjected to analysis according to author, year, study objectives, type of diabetes, reference time period, geographical coverage (country), data source, reported metrics (DALY, YLD, YLL, incidence, prevalence, mortality), and program used. The articles that met the inclusion criteria were then organized in Microsoft Excel. Eligibility assessments were conducted in accordance with the inclusion and exclusion criteria established for each study.

RESULTS

Figure 1 presents the search flow chart of available burden of disease studies and an overview of the search and screening strategy performed in the literature review, including the main reasons for exclusion. Initially, a total of 1,307 studies were identified from the following databases: MEDLINE (n=404), Scopus (n=721), ScienceDirect (n=162), BioMed Central (n=14), and CINAHL (n=6). Following the removal of 208 duplicates, a total of 1,099 studies were retrieved for title abstract search in the Mendeley database. Following the removal of 836 studies upon title and abstract screening, 125 studies were subjected to a further evaluation process to ascertain their eligibility. Following a comprehensive review of the extant literature, a total of 16 eligible studies were included in the present research.

The PRISMA flow diagram showing the research inclusion process and reasons for exclusion is presented in Figure 1.

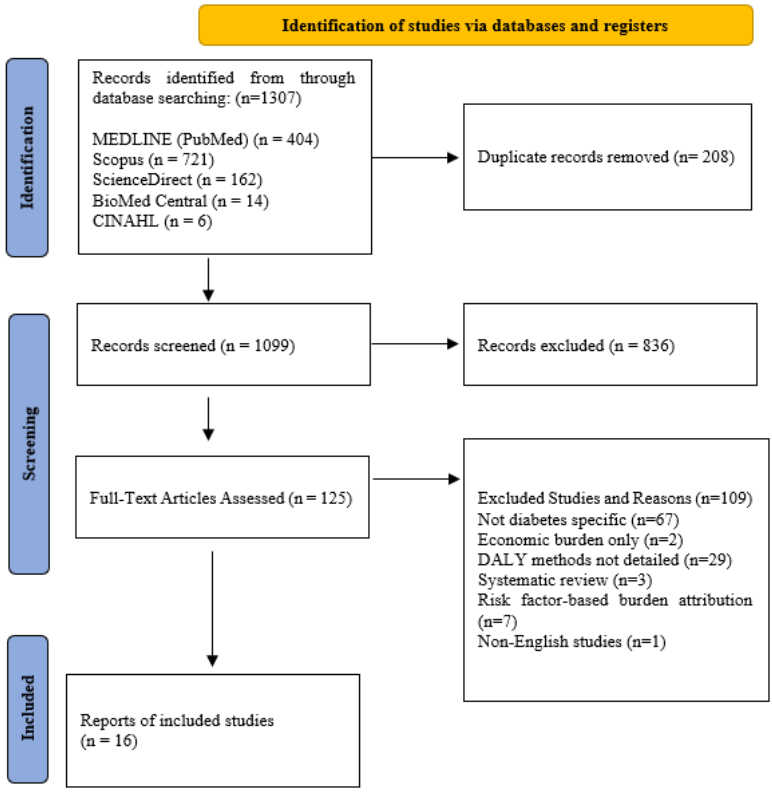

Figure 1. PRISMA flow chart for study selection

Study Characteristics

The objective of all studies included in the review was to assess or estimate the impact, burden and outcome of diabetes (see Table 3), and DALYs were utilized as a measure of diabetes disease burden. DALYs were expressed as years lost per 100,000 population. Of the 16 studies ultimately identified, five (Kotwas et al., 2021; Luo et al., 2024; Sun et al., 2023; Yang et al., 2024; Zhu et al., 2022) encompassed global coverage, while the remaining studies were conducted in the Western Pacific (Cao et al., 2023), North Africa and the Middle East (Esmaeili et al., 2022), and Latin America (Ilic & Ilic, 2024). A total of eight studies (Bandarian et al., 2023; Bener et al., 2014; Dávila-Cervantes, 2023; Oliveira et al., 2009; Gonzalez et al., 2014; Islam et al., 2023; Liu et al., 2023;

Pandey et al., 2022) assessed the effects of diabetes disease burden in a single country (Iran, Qatar, Mexico, Brazil, Argentina, Australia, China, and Nepal).

Table 3: An overview of diabetes burden of disease studies

Authors, Year	The Studies' Aims and Objectives	Type	Reference Time Period	Geographic Coverage	Data Source	Reported Metric(s)	Used Analysis Methods
(Bandarian et al., 2023)	'Estimating the burden of T1 DM in Iran over the last 30 years by sex, age, year, and state'	T1DM	1990-2019	Iran (31 states)	GBD 2019	DALYs, YLDs, YLLs, Incidence, Prevalence, Mortality	Stata version 13/R version 3.5.0
(Bener et al., 2014)	'To quantify the burden of disease in terms of deaths and DALYs due to DM in the State of Qatar'	DM	2007-2011	Qatar	ICD-10 mortality data (2013)/ Life tables (2007)/ Health records/ Databases/ Surveys	DALYs, YLDs, YLLs, Incidence, Prevalence, Mortality	Not reported
(Cao et al., 2023)	'To identify DM regional burden, trends, and inequalities in the Western Pacific region'	DM	1990-2019	West Pacific	GBD 2019	DALYs, Incidence, Prevalence, Mortality	GraphPad Prism (8.0), R software (1106), Joinpoint Regression 4.9.0.0
(Dávilla-Cervantes, 2023)	'Analysing the findings of the T2DM GBD-2019 study in adolescents and young adults'	T2DM	1990-2019	Mexican	GBD 2019	DALYs, YLDs, YLLs	Joinpoint Regression 4.8.0.1
(Oliveira et al., 2009)	'Presenting disease burden results in Brazil with emphasis on DM and its complications'	DM	1998	Brazil	ICD-10/ National Death Information System/SIM/ SUS/	DALYs, YLLs, YLDs, Mortality	Not reported
(Esmaeili et al., 2022)	'Reporting the burden of T1DM in the North Africa and MENA region and 21 countries'	T1DM	1990-2020	North Africa and MENA	GBD 2019	DALYs, YLDs, YLLs, Incidence, Prevalence	R software (version 3.6.1)

(Gonzalez et al., 2014)	'Measuring the economic burden of DM in Argentina by age, sex and region, in DALYs'	DM	2005	Argentina	Victorian Burden of Disease study, Office for National Statistics (2005), QUALIDIAB records, IDMPS study, Muray and Lopez 1996	DALYs, YLLs, YLDs	Not reported
(Ilic & Ilic, 2024)	'Assessing the burden of T2DM in Latin America'	T2DM	1990-2019	Latin America	GBD 2019	DALYs, Incidence, Mortality, YLDs, YLLs	Joinpoint software 4.9.0.0, SPSS software 20.0
(Islam et al., 2023)	'Comparing T2DM morbidity and mortality trends with countries with similar SDI'	T2DM	1990-2019	Australia	GBD 2019	DALYs, Prevalence, YLLs, YLDs, Mortality	Not reported
(Kotwas et al., 2021)	'Analysing selected epidemiological factors for T2DM'	T2DM	2000-2019	Poland, CE and Global	GBD 2019	DALYs, YLLs, YLDs	Not reported
(Liu et al., 2024)	'To comprehensively examine the temporal trend of DM DALYs from a global perspective'	DM	1990-2019	China	GBD 2019	DALYs, Incidence, Prevalence, Mortality	R v3.5.1
(Luo et al., 2024)	'Assessing the burden of T2DM in adolescents (15-24 years)'	T2DM	1990-2019	Global	GBD 2019	DALYs, Incidence	R software (version 4.1.1)
(Pandey et al., 2022)	'To present the burden of DM in terms of prevalence, mortality, and DALY'	DM	1990-2019	Nepal	GBD 2019	DALYs, Prevalence, Mortality	Not reported
(Sun et al., 2023)	'To assess DM globally and by different subgroups and to estimate the future burden of disease'	DM	1990-2019	Global	GBD 2019	DALYs, Incidence, Prevalence, Mortality	R 4.0.2, Microsoft Office Excel 2019, IBM SPSS 20.0

(Yang et al., 2024)	'To estimate the burden, trends, and inequalities of T1DM in older adults at global, regional, and national levels'	T1DM	1990-2019	Global	GBD 2019	DALYs, Prevalence, Mortality	GraphPad Prism 8.0, Joinpoint Regression program 5.0.2, and R 4.2.3
(Zhu et al., 2022)	'Examining descriptive epidemiology and trends in the burden of T2DM'	T2DM	1990-2019	Global	GBD 2019	DALYs, Incidence, Mortality	R software (version 3.5.1)

Abbreviations: DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; DALYs, disability-adjusted life years; YLDs, years lived with disability; YLLs, years of life lost; GBD, Global Burden of Disease; MENA, Middle East and North Africa; CE, Central Europe.

Three of the studies (Bener et al., 2014; Gonzalez et al., 2014; Oliveira et al., 2009) estimated the burden of disease by calculating their own DALYs, YLDs, or YLLs, while 13 were secondary analyses using GBD 2019 results. In the context of the present study, a comprehensive review of the extant literature reveals those nine of the sixteen studies (Bandarian et al., 2023; Bener et al., 2014; Dávilla-Cervantes, 2023; Esmaeili et al., 2022; Gonzalez et al., 2014; Ilic & Ilic, 2024; Islam et al., 2023; Kotwas et al., 2021; Oliveira et al., 2009). In three studies (Cao et al., 2023; Liu et al., 2024; Sun et al., 2023) combined DALY (disability-adjusted life year) metrics, whilst three further studies (Cao et al., 2023; Liu et al., 2024; Sun et al., 2023) combined DALY with incidence, prevalence, and mortality data. Two of the remaining four studies (Pandey et al., 2022; Yang et al., 2024) utilized DALY, prevalence, and mortality data, one study (Zhu et al., 2022) incorporated DALY and incidence and mortality data, and the final study (Luo et al., 2024) encompassed solely DALY and incidence data.

The time intervals illustrated in Figure 2 denote the years in which the included studies were published. The highest number of studies was documented in 2023 (Bandarian et al., 2023; Cao et al., 2023; Dávilla-Cervantes, 2023; Islam et al., 2023; Sun et al., 2023).

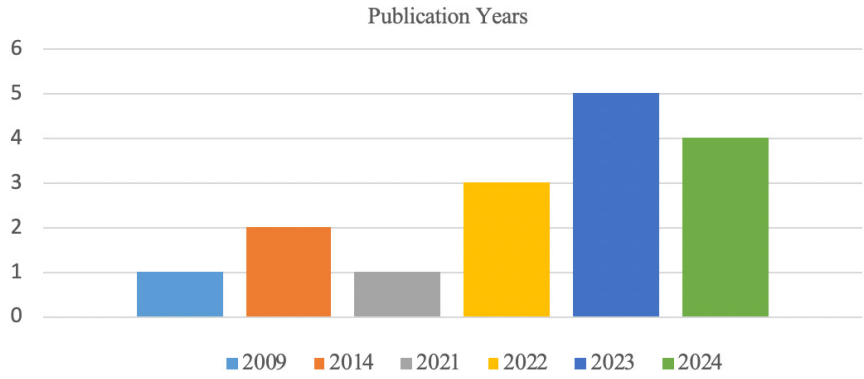

Figure 2. Years of publication of diabetes burden of disease studies

The time intervals illustrated in Figure 2 denote the years in which the included studies were published. The highest number of studies was documented in 2023 (Bandarian et al., 2023; Cao et al., 2023; Dávilla-Cervantes, 2023; Islam et al., 2023; Sun et al., 2023). In 2024, four studies were published (Ilic & Ilic, 2024; Liu et al., 2024; Luo et al., 2024; Yang et al., 2024). In 2022, three studies were published (Esmaelili et al., 2022; Pandey et al., 2022; Zhu et al., 2022). Additionally, one study was published in 2021 (Kotwas et al., 2021), two in 2014 (Bener et al., 2014; Gonzalez et al., 2014), and one in 2009 (Oliveira et al., 2009).

The findings related to author, year, age, weighting, morbidity, mortality, and DALY data from the included studies according to the search criteria are presented in Table 4.

Table 4: Evaluation results of diabetes burden studies

Authors, Year	Age Weighting	Morbidity			Mortality		DALYs (UI 95%)	DALYs Change Rate
		YLDs (UI 95%)	Prevalence	Incidence	Mortality	YLLs		
(Bandarian et al., 2023)	✓	28.2	388.9	11	0.7	23.5	51.7	4.7%
(Bener et al., 2014)	-	3.57	-	-	-	0.79	4.35	-
(Cao et al., 2023)	✓	-	T1DM=146.5 T2DM=4583.5	T1DM=3.8 T2DM=207.3	T1DM=0.4 T2DM=10.4	-	T1DM=27.4 T2DM=526.7	-
(Dávilla-Cervantes, 2023)	✓	195.44	-	-	2.47	168.0	342.88	31.29%
(Oliveira et al., 2009)	-	72.5	-	-	0.3	27.5	5.1	29.6%
(Esmaeili et al., 2022)	✓	26.6	378.5	10.6	1.2	37.4	64	71.6%
(Gonzalez et al., 2014)	✓	693.244	-	-	39.751	101.116	794.360	-
(Ilic & Ilic, 2024)	✓	559.2	-	313.0	29.9	610.0	1169.2	0.2%
(Islam et al., 2023)	✓	284.3	3429.9	-	8.9	140.4	424.8	17.0%
(Kotwas et al., 2021)	✓	GL: 423.72 CE: 513.46 PL: 516.33	-	-	-	GL:377.8CE:216.77 PL:191.89	GL:801.5CE:730.22 PL:708.22	GL:16.3% CE:24.7% PL:32.6%
(Liu et al., 2024)	✓	-	GL:8.827 China: 8.170	GL:416 China: 329	GL:30 China:15	-	GL:8.572.039 China:2.498.315	GL:20.3% China:43.7%
(Luo et al., 2024)	✓	-	-	108.36	-	-	49.20	2.01%
(Pandey et al., 2022)	✓	-	5.735.58	-	19.57	-	348	-
(Sun et al., 2023)	✓	-	5.555.39	267.54	19.47	-	858.96	0.71%
(Yang et al., 2024)	✓	-	514	-	3.54	-	103	- 33%
(Zhu et al., 2022)	✓	-	-	259.94	18.49	-	801.55	1.43%

An examination of Table 4 in the study by Bandarian et al. (2023) reveals an investigation into T1DM on a provincial basis in Iran. The study reported an increase in the average annual trend of age-standardised DALYs of 4.7% (95% CI - 11.2 to -23.3) between 1990 and 2019. Esmaeili et al. (2022) also examined the burden of T1DM disease in the North African and Middle Eastern region. The present study concluded that the age-standardised DALY rate increased by 71.6% (95% CI 43.9 to 99.9) over the last 30 years. The highest level of DALY annual rate of change was identified in the study by Esmaeili et al. (2022). A further study that examined T1DM was conducted by Yang et al. (2024). This study focused on the global population aged 65 years and over, and it was found that there was a decrease in the age-standardized DALY rate by -33% (95% CI -0.41% to -0.25%).

In the T2DM burden study conducted by Dávilla-Cervantes (2023) on adolescents and young adults, it was found that the age-standardized DALY rate increased by 31.29% (95% CI 17.52 to 48.75) between 1990 and 2019. In the study conducted by Ilic and Ilic (2024), the DALY rate due to T2DM in Latin America from 1990 to 2019 demonstrated a significant increasing trend (0.2% [95% CI 0.2 to 0.3]). In their study on the burden of T2DM in Australia, Islam et al. (2023) found that age-standardized DALYs increased by 17.0% (95% CI 5.0% to 29.9%). Zhu et al. (2022) found that the DALY rate increased by 1.43% (1.28 to 1.58) in the type 2 diabetes burden study conducted on the global population. Luo et al. (2024) found that from 1990 to 2019, the age-standardized DALY rate of T2DM in adolescents showed an increasing trend of 2.01%. In their seminal study, Kotwas et al. (2021) examined the burden of T2DM in Poland, Central Europe, and globally. Their findings revealed a significant increase in the age-standardized DALY rate, with increases of 16.37% on a global scale, 24.73% in Central Europe, and 32.65% in Poland.

The study conducted by Liu et al. (2024) on individuals with DM aged ≥ 20 years in China and globally found the highest age-standardized DALY rate to be 2.498.315. Consequently, the contribution of aging to diabetes DALYs was found to be significantly higher in China (43.7%) compared to the global average (20.3%). Sun et al. (2023), demonstrated that the global burden of disease attributable to diabetes has exhibited a marked upward trajectory since 1990, with an observed increase of 0.71% (95% CI 0.67 to 0.75). In the diabetes burden of disease study conducted by Oliveira et al. (2009), it was stated that there will be an increase of 29.6% in 15 years (1998-2013).

DISCUSSION AND CONCLUSIONS

This systematic review provides a comprehensive synthesis of studies that assess the burden of diabetes in terms of DALYs. Notably, 13 out of the 16 studies included relied on secondary analyses of GBD data, which highlights the dominance of the GBD framework as the primary source for global and national burden estimations. Using standardized GBD data across most of the studies included ensures methodological consistency and enables meaningful comparisons of the burden of diabetes across countries and over time. This review provides an overview of studies that have utilized and estimated DALYs

from diabetes as a health impact assessment technique. The objective of this study was to identify studies that examined the global, national, and regional burden of diabetes disease, and to identify the epidemiological measures (DALYs, YLD, YLL, incidence, prevalence, and mortality) and methods used. Following a comprehensive analysis of 1,307 studies, 16 studies were deemed to meet the established eligibility criteria. The DALY metric was expressed as years lost per 100,000 population. Seven of these studies evaluated the effects of a single country. Five of the studies were analyzed in a global dimension. In the studies conducted in China and Poland, both national and global impacts were analyzed and compared. Other studies were carried out across regions, including the Western Pacific, North Africa and the Middle East, and Latin America.

Seven studies addressed diabetes in general, while the remaining six studies addressed type 2 diabetes and three studies addressed type 1 diabetes exclusively. As a reference time frame, 12 studies made a 30-year estimate between 1990 and 2019. Of the 16 studies, nine employed DALY, YLD, and YLL metrics in conjunction, three utilized DALY with incidence, prevalence, and mortality data, two employed DALY, prevalence, and mortality data, one employed DALY with incidence and mortality data, and one employed solely DALY and incidence data. The analysis program utilized was predominantly R and Jointpoint Regression methods, while six studies did not specify the method employed. An evaluation of the study's results across different regions has revealed significant variations. For instance, while Esmaeili et al. (2022) reported a 71.6% increase in the type 1 diabetes burden in North Africa and the Middle East, Yang et al. (2024) noted a 33% decrease in DALY rates among older adults, suggesting improvements in disease management for this age group. In a similar fashion, Latin America (Ilic & Ilic, 2024) and Australia (Islam et al., 2023) exhibited rising trends, albeit at differing rates. The nation of China (Liu et al., 2024) bore the greatest DALY burden in general, primarily as a consequence of its aging population.

The observed variation in DALY trends across countries and diabetes types reflects differences in health system performance, demographic transitions, prevalence of risk factors, and methodological choices in burden estimation. For instance, the considerable rise in type 1 diabetes DALYs in North Africa and the Middle East stands in stark contrast to the declining trends observed

among older adults worldwide. This finding indicates the presence of regional disparities in disease control and access to healthcare services. These findings are consistent with systematic reviews of disease burden in other domains, such as cardiovascular diseases and chronic non-communicable rare diseases, which also report substantial heterogeneity in burden estimates despite similar methodologies (Charalampous et al., 2022; Oliveira et al., 2024).

Three of the included studies estimated the disease burden by directly calculating DALYs, YLLs, or YLDs using their own national data and methodologies. For instance, Dávilla-Cervantes (2023) conducted an age-specific burden analysis among adolescents and young adults in Mexico, revealing a 31.3% increase in DALY rate for type 2 diabetes in this demographic. Conversely, 13 studies utilized secondary analysis of GBD 2019 data. The extensive utilization of GBD estimates, as evidenced in Liu et al. (2024) for China and Ilic & Ilic (2024) for Latin America, confers the benefit of methodological standardization and facilitates valid comparisons across nations and over time. However, it also underscores a growing reliance on modelled data. Furthermore, in numerous GBD-based studies, including Islam et al. (2023), the analytical methods and statistical programs employed were not explicitly delineated, impeding transparency and reproducibility. It is imperative to articulate the methodologies employed to ensure transparency, comparability, and interpretability of future study outcomes. This study also underscores the absence of harmonization of epidemiological data and methods, which hinders the capacity for meaningful comparisons between studies of diabetes. It is recommended that studies be conducted in a range of countries and regions, particularly for global analysis.

Research into the epidemiological aspects of diabetes, which determine the burden of the disease and its impact on the healthcare system, helps policymakers and healthcare providers to determine their priorities for action and resource allocation. Consequently, this research is considered significant in terms of providing information on diabetes burden studies. The generation of further DALY study estimates could raise awareness of the necessity for research into diabetes and the allocation of social support funding, thereby reducing the burden of diabetes and inequalities. In this context, it is recommended that further high-quality studies be conducted, such as meta-analyses on the burden of diabetes.

Strengths and Limitations

To the best of our knowledge, this is the first systematic review to focus exclusively on the disease burden of diabetes using DALY, YLD, and YLL metrics. The use of standardised GBD data and adherence to PRISMA guidelines enhance comparability, transparency, and reproducibility. This review has several limitations. Only English-language studies were included, which may introduce language bias. Furthermore, the search was limited to specific databases (MEDLINE, Scopus, ScienceDirect, BioMed Central, and EBSCO). Lastly, methodological variations across studies, such as differences in data sources and DALY calculation methods, may limit the direct comparability of the findings.

Ethical Approval: Authors declare that the study presented in the manuscript entitled "A systematic review of the burden of disease studies on diabetes" does not require ethical approval.

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The Right of International Students to Access Healthcare in Practice and Turkish Legal Legislation

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ABSTRACT

The subject of this study is the right of international students studying in Türkiye to access healthcare services. The study examines the healthcare access processes of international students in Türkiye within the framework of both normative (legal) regulations and practical challenges. The main focus of the research is on how international students benefit from healthcare services during their educational journey, the legal foundations of this process, and the structural barriers encountered in practice. This study aims to present the legal regulations regarding the right to health for international students in Türkiye and to analyze how these regulations are implemented in practice, thereby identifying existing structural problem areas. Particular emphasis is placed on how elements such as bureaucratic complexity in health insurance procedures, language barriers, and lack of information restrict students' access to this right. The significance of this study stems from the fact that the effectiveness of services provided to international students within the framework of Türkiye's higher education internationalization policies is directly related to their access to healthcare services. When equal and effective access to the right to health

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cannot be ensured, not only do individual grievances arise, but Türkiye's inclusive vision in international education is also weakened. Therefore, this issue is not merely a matter of healthcare provision but also has strategic importance in terms of educational policies and foreign policy. In this study, a qualitative research methodology has been adopted, and legal documents, official reports, and policy papers have been examined thematically. Through this method, the discrepancies between legal regulations and actual practice have been systematically revealed.

Keywords: Healthcare Access, Higher Education Policies, International Students, Right to Health, Türkiye

INTRODUCTION

Current literature demonstrates that international students have the opportunity to explore different cultures, expand their capacity for critical thinking, and develop intercultural knowledge and skills, while also providing both material and non-material contributions to the countries they travel to for educational purposes (Contreras-Aguirre & Gonzalez, 2017; Wu et al., 2015). These students contribute to the development of the host countries in various social, economic, and cultural aspects, leading states to adopt internationalization policies driven by the desire to benefit from such contributions. Internationalization policies serve as both a strategy aimed at students during the process of cultural exchange and education, and as a tool to enhance the host country's competitiveness in the international arena and promote cultural diversity.

In an environment characterized by cultural diversity, the presence of international students offers an opportunity to further strengthen understanding and tolerance. Internationalization policies foster social cohesion in the host country, enabling the education system to meet global standards and enhance the host country's international standing. According to Akıllı (2023), states in the international system employ various strategies and tools to effectively conduct their foreign policies. One of the most important elements that enhances the legitimacy of a state's foreign policy is public diplomacy. Public diplomacy encompasses all efforts by states to promote themselves internationally, disseminate their cultural values, and build

credibility. Education is considered a functional component of soft power strategies, which are among the driving forces behind internationalization policies. Particularly in the field of higher education, states gain the opportunity to create a positive image through the international students they host. These students contribute to increasing the international influence of host countries by reflecting the quality and cultural diversity of the education systems they experience. In this way, countries have the potential to reinforce the legitimacy of their foreign policies through the opportunities they offer in the field of education.

The economic contributions of international students to their host countries are also noteworthy (Andrade, 2009; Wu et al., 2015). By adopting the consumption habits of the countries in which they study and establishing social interactions, these students provide significant inputs to local economies. These contributions support the economic growth of states, enhance their competitiveness on the international stage, and contribute to overall economic development. In other words, international education is not only a tool for promoting cultural and social interactions, but also a strategic element that holds the potential to strengthen states' international legitimacy and generate economic benefits. By reinforcing their policies in this area, states aim to attain a more influential position in international relations.

Access to healthcare services for international students, who contribute to states culturally, diplomatically, and economically, is a key dynamic of internationalization policies, as healthcare access directly affects international students' experiences in host countries and the extent to which they can contribute to their home countries.

According to the Republic of Türkiye Ministry of Interior Presidency of Migration Management (2022), the healthcare system in Türkiye has a comprehensive and multi-dimensional structure with extensive services. In order to benefit from healthcare services, individuals are required to have either private health insurance or general health insurance. Those without insurance can still access healthcare services by paying a fee. International students also access healthcare through general health insurance, and this system is supported by both private institutions and public organizations.

Within the framework of internationalization policies, the level of access to healthcare services stands out as a factor that not only influences international students' academic and social experiences but also serves the interests of the host country. Although fair and effective access to healthcare plays a critical role in enabling students to successfully pursue their education and integrate into the society they live in—and is legally recognized as a right—it does not always function smoothly or equitably in practice. The right to access healthcare is often intertwined with numerous obstacles, such as the interpretability of administrative regulations, language barriers, the complexity of the enrollment process, and a lack of adequate information. This situation creates a gap between the healthcare coverage that international students legally possess and the healthcare benefits they receive in practice.

This study assumes that the various inequalities international students face in accessing healthcare services not only lead to individual grievances but also call into question the inclusivity claims embedded in internationalization policies. Accordingly, the main aim of this study is to analyze the right to health of international students who come to Türkiye for educational purposes within the legal framework and to reveal structural problem areas by evaluating how this framework is implemented in practice. Aiming to interpret both the normative basis and administrative practices related to international students' right to health, this study examines the rights-based dimension of existing policies by referring to the constitution, social security legislation, public institution reports, and national strategy documents.

METHODOLOGY

This study is structured following a qualitative research methodology and aims to analyze the structural issues international students encounter in accessing healthcare services in Türkiye, along with the practical implications of existing legal regulations. A descriptive and interpretive approach is adopted, and the research is based not on direct individual participation, but on the systematic examination of normative documents and publicly available administrative materials concerning the right to health for international students. The primary data sources of the study include the Constitution of the Republic of Türkiye, Social Insurance and General Health Insurance Law, official

reports published by the Republic of Türkiye Ministry of Interior Presidency of Migration Management, internationalization strategy documents issued by the Council of Higher Education, and policy texts from the Republic of Türkiye Ministry of Health and other relevant public institutions. The selection of these documents is based on criteria such as relevance to the research objective, currency, and reliability. The primary criterion of the study is the scope of legal regulations regarding the right to health and how these are reflected in practice. Secondary criteria include academic sources and public reports that reveal inequalities observed in implementation. Content analysis is used as a method of data analysis, with documents thematically coded under headings such as "legal rights", "insurance coverage", "implementation disparities", "language barriers", "lack of information", and "complex administrative procedures". Following the coding process, these themes are comparatively analyzed to identify discrepancies between the normative framework and actual practice. The research does not involve quantitative statistical analyses, and the interpretations rely on qualitative data analysis techniques. As the study does not involve direct interaction with individuals or fieldwork, it does not require ethical board approval. All sources used are publicly accessible documents, and full compliance with academic ethical standards is maintained throughout the research process.

International Students and Access to Healthcare Services

The health rights of international students and their access to healthcare services are becoming increasingly important. Augoustinos et al. (2011) state that international students report lower levels of health and well-being. Studies indicate that students face issues such as cultural stigma, language barriers, and long waiting times. These challenges have negative effects on students' overall health and well-being (LaMontagne et al., 2023).

International students encounter various challenges that affect their physical and psychological health while adapting to a new country (Augoustinos et al., 2011; Rienties et al., 2012). These health-related challenges are often perceived as less significant compared to other difficulties they face (Mesidor & Sly, 2016; Skromanis et al., 2018). On the other hand, these students are often unable to fully benefit from local healthcare services. In many countries, international

students face barriers to accessing healthcare, do not receive adequate benefits from existing services, and delay seeking medical attention when ill (Martin & Dyer, 2017). The fear of stigma also makes it difficult for them to access health services (Vidourek et al., 2014). Additionally, healthcare providers in host countries experience difficulties in serving international students due to linguistic mismatches, cultural differences, and resource constraints (Jaeger et al., 2019).

Newton et al. (2021), by examining the existing opportunities and challenges for improving the health and well-being of international students, revealed that nearly all international students perceive their health and well-being as a holistic concept that includes both physical and mental/emotional health. This finding contributes to a better understanding of the barriers students face in accessing healthcare services and enables the development of necessary strategies to overcome these obstacles. The study by Citak Tunc et al. (2021), which investigates the relationship between international students' health perceptions and healthy lifestyle behaviors, demonstrates that students' perceptions of health significantly influence their engagement in healthy lifestyle practices. Similarly, study by Akinola (2014), highlight the health problems faced by international students and affirm the need for the development of healthcare services and programs to support their well-being throughout their education. As emphasized in this study, the effective protection of the right to health is of critical importance for international students to maintain a healthy life.

Studies focusing on the mental health of international students emphasize that these students face challenges such as isolation, language barriers, financial stress, and academic pressures (Hyun et al., 2007; Mori, 2000). These difficulties are noted to potentially hinder students' access to healthcare services (Forbes-Mewett & Sawyer, 2016; Mori, 2000; Skromanis et al., 2018).

The right to health for international students also includes access to sexual and reproductive health services. Poljski et al. (2014) analyzed the experiences of female international students in accessing information and services related to sexual and reproductive health and reported that they were not treated equally compared to males. This finding highlights that access to healthcare services should be addressed not only in physical terms but also through its social and cultural dimensions. The challenges faced in accessing sexual

and reproductive health services reflect broader issues within the overall healthcare access experience of international students. Skromanis et al. (2018) stated that male international students reported lower levels of satisfaction and exhibited lower health-seeking behavior compared to females. This issue of gender-based inequality in access to healthcare once again underscores the social significance of the right to health. Moreover, access to healthcare should be considered not only in terms of students' well-being but also as a broader factor influencing their social and academic lives.

International students, who must adapt to their new roles, share common stress factors such as family-related pressures, scholarship requirements, financial burdens, and academic challenges (Misra & Castillo, 2004). The stress of transitioning to university life for international students is compounded by additional stressors related to learning the culture of a new country (Xiaoqiong, 2008). Moreover, students face multifaceted challenges such as language difficulties, racism, discrimination, social isolation, and financial problems. These factors make them vulnerable to potential health issues (Burt et al., 2017; Cheng, 2004; Lee, 2014; Sherry et al., 2010).

Rosenthal et al. (2008) state that the most common reason students do not seek healthcare services is that they do not perceive their problems as serious enough. The authors identify four main factors influencing this situation: lack of knowledge about healthcare services, location or availability of services, appointment procedures, and uncertainties regarding fees. Hyun et al. (2007) and Mori (2000) state that the lower likelihood of international students accessing healthcare services is linked to poor health literacy, which supports these four factors (Poyrazli & Grahame, 2007). Health literacy is defined as the ability of patients to obtain, process, communicate, and understand essential health information and services necessary to make appropriate health decisions. Health literacy is a dynamic concept because an individual's health literacy may vary depending on the medical condition being treated, the healthcare provider, and the system delivering care (Baker, 2006). To make appropriate health decisions, individuals need to find health information, evaluate it in terms of reliability and quality, and analyze its risks and benefits (U.S. Department of Health and Human Services Office of Disease Prevention and Health Promotion [ODPHP], 2010).

Health literacy is explained by Baker (2006) as a conceptual model consisting of two main domains. The first involves the ability to effectively use healthcare personnel and systems to gain access to healthcare rights, while the second encompasses the skills to understand and use printed, and oral texts related to health. Health literacy is shaped by both individual characteristics and the healthcare system and directly impacts an individual's health status (Baker, 2006). Low health literacy can negatively affect health outcomes by preventing individuals from effectively utilizing the healthcare system.

Low health literacy has been associated with poorer health outcomes, including different patterns of healthcare service use, increased hospitalizations, greater emergency care visits, reduced medication adherence, and difficulties interpreting medication labels and health messages (Berkman et al., 2011; Greenhalgh, 2015). It is more prevalent among low-income individuals, ethnic minorities, immigrants, those whose first language is not the dominant language, less-educated populations, and older adults (Greenhalgh, 2015). Even well-educated individuals with high health literacy may struggle to navigate the complexities of healthcare terminology and procedures (Cornett, 2009). Within this context, the challenges international students face in accessing healthcare services further highlight the importance of support mechanisms provided by states.

Access to Healthcare Services for International Students in Türkiye

As one of the countries with a rapidly increasing number of international students, Türkiye has developed various policies aimed at protecting and/or facilitating students' access to healthcare services. However, language barriers, adaptation challenges, and lack of information about rights make it difficult for international students to benefit from healthcare services. Although there is a relatively extensive body of research on the use of healthcare services by migrants in Türkiye, studies focusing specifically on international students' access to and utilization of healthcare services are quite limited (Masai et al., 2021). To better understand these problem areas, it is necessary first to outline the existing constitutional and legal regulations. At this point, an evaluation should be made not only in terms of national legal frameworks but also considering the international human rights documents to which Türkiye is a party.

Article 2 of the International Covenant on Economic, Social and Cultural Rights (ICESCR), to which Türkiye is a party, stipulates that the rights recognized by the covenant must be guaranteed to all individuals without discrimination based on "race, color, sex, language, religion, political or other opinions, national or social origin, property, birth or other status." Similarly, Article 12 defines the right of everyone to the highest attainable standard of health and imposes an obligation on states to take the necessary measures to achieve this right (International Covenant on Economic, Social and Cultural Rights [ICESCR], 1966). Article 11 of the European Social Charter (CoE) likewise provides that access to health care must be ensured by public authorities (Council of Europe, 1996). Under these provisions, Türkiye is obliged to establish the necessary administrative and financial arrangements to ensure that international students can equally and effectively benefit from healthcare services. In particular, Article 12 of the ICESCR recognizes everyone's right to the highest attainable standard of health. Therefore, this normative framework requires that national legislation and practices be compatible with international obligations. The counterpart of this normative framework in national law is the Constitution of the Republic of Türkiye.

Article 56 of the Constitution of the Republic of Türkiye states that "everyone has the right to live in a healthy and balanced environment", while Article 10 emphasizes that "no person, group, or class shall be granted privileges", expressing that access to health services should be provided without discrimination (Constitution of the Republic of Türkiye, 1982). The concept of "everyone" in the Constitution is interpreted in legal doctrine and the Constitutional Court of the Republic of Türkiye jurisprudence as encompassing not only Turkish citizens but all individuals within Türkiye's jurisdiction (Tanör & Yüzbaşıoğlu, 2018). In this context, even international students who hold temporary status have constitutional guarantees regarding the right to health; however, the practical implementation of these normative guarantees remains open to debate. In other words, whether these constitutionally recognized rights are applied equally in administrative practices emerges as an important issue. Particularly, the tendency to prioritize citizens in the planning of health services may limit the extent to which international students can benefit from these rights. Therefore, there appears to be a gap between constitutional guarantees

and administrative practices. This situation indicates that legal regulations alone are insufficient and that universities must also play a significant role in practice. Universities bear important responsibilities, especially during this process.

The effective utilization of health services by international students is directly related not only to legal regulations but also to the practices of educational institutions in this area. Citak Tunc et al. (2021) emphasize that taking necessary measures, providing guidance services, and collecting data about international students are among the responsibilities of educational institutions to ensure these students can successfully continue their education. In this context, systematic efforts carried out by universities will not only enhance academic success but also strengthen students' capacity to exercise their health rights. To identify healthy lifestyle behaviors, it is essential first to review international students' perceptions of health. Researching to determine the health and health responsibility perceptions of students currently studying or newly enrolled at universities has become a necessity. Within this framework, universities make agreements with various insurance companies to offer students affordable and comprehensive health insurance options. During this process, students are not only presented with insurance options but are also informed about health insurance procedures and supported in obtaining necessary documents. The information that international students need to have regarding seeking and receiving health services can be provided during international student orientation. During this orientation, students receive information about expected behaviors, norms, and rules to help them adapt to the culture and university life, and they are also guided through the documentation process (Fischer, 2011). In this way, universities not only contribute to fulfilling legal obligations but also take on a proactive role in ensuring that students can effectively benefit from health services.

Following the constitutional and international normative framework, regulations that enable the exercise of the right to health can be addressed. Health insurance regulations demonstrate the legal instruments through which students can exercise their right to health. In order for international students to benefit from health services, they must first have valid health insurance. International students studying in Türkiye are required to obtain

health insurance for the duration of their education. This obligation is critically important for facilitating international students' access to health services and enabling them to cope with potential health issues. Students can complete health insurance procedures through their registered educational institutions, where they can also receive necessary information and support services (Social Security Institution [SGK], 2014). Health insurance reduces the financial burden in cases of emergencies or health problems requiring treatment, thus allowing students to pursue their education with greater security. However, in practice, the registration process for General Health Insurance can be complicated for some students due to bureaucratic complexities, language barriers, and lack of adequate information, making it difficult for them to manage the process effectively. This situation may prevent the full practical utilization of the right to health as defined at the constitutional level.

Before addressing regulations related to health insurance, it is necessary to present the legal provisions that define the legal status of international students in Türkiye. In this context, the regulations determining the legal status of international students in Türkiye gain importance. Article 3 of Law No. 5978 on the Organization and Duties of the Presidency for Turks Abroad and Related Communities, dated March 24, 2010, defines a foreign student as "those who are deemed appropriate by public institutions and organizations to receive education in our country, as well as foreign nationals who come to Türkiye for educational purposes within the framework of international agreements." (Yurtdışı Türkler ve Akraba Topluluklar Başkanlığı Teşkilat ve Görevleri Hakkında Kanun, 2010). With the enactment of the Law on Foreign Nationals Studying in Türkiye, the provisions of Law No. 2922 concerning scholarships for foreign students have become invalid (Türkiye'de Öğrenim Gören Yabancı Uyruklu Öğrencilere İlişkin Kanun, 1983). This regulation not only defines international students but also outlines their legal status in Türkiye, thereby laying the groundwork for the subsequent health insurance regulations.

Law No. 2922 is a legal framework that regulates the scholarship opportunities and educational processes available to foreign nationals who come to Türkiye for educational purposes. While this law provides state-supported scholarships and accommodation opportunities to a limited number of foreign students, its

scope is narrow. In this respect, the law is insufficient in addressing the growing needs arising from the increasing number of international students. Law No. 5978, which offers a broader definition of foreign students, goes beyond merely regulating scholarships and encourages the establishment of the Presidency for Turks Abroad and Related Communities to enable the coordinated management of services for foreign students. During the period of Law No. 2922, responsibilities were carried out by the Ministry of National Education and the Council of Higher Education, whereas under Law No. 5978, these duties have been consolidated under a single institution, creating a more effective administrative mechanism. This change, aimed at transforming Türkiye into an international education hub, seeks to improve the quality of education that students receive during their stay in Türkiye and to contribute to internationalization policies from this perspective.

Another legal regulation concerns health insurance. According to the seventh paragraph added to Article 60 of Law No. 5510 by Article 34 of Law No. 6111, there is an obligation to obtain General Health Insurance based on thirty days calculated at one-third of the minimum daily earnings subject to premiums, in accordance with the Law on Higher Education No. 2547 (Bazı Alacakların Yeniden Yapılandırılması ile Sosyal Sigortalar ve Genel Sağlık Sigortası Kanunu ve Diğer Bazı Kanun ve Kanun Hükmünde Kararnamelerde Değişiklik Yapılması Hakkında Kanun, 2011; Yükseköğretim Kanunu, 1981). Health expenses of international students are also covered by additional allowances allocated to university budgets under Articles 46 and 47 of Law No. 2547. Despite all these provisions, students coming from countries that have social security agreements with Türkiye can be exempted from the General Health Insurance if they have insurance in their own country and document this with a "health assistance entitlement certificate" (Baş & Eti, 2020).

Law No. 6486 is a significant step toward facilitating international students' access to healthcare services in Türkiye. This regulation has made the health insurance system more accessible for international students and established the necessary framework for them to effectively benefit from health services (Sosyal Sigortalar ve Genel Sağlık Sigortası Kanunu ile Bazı Kanunlarda Değişiklik Yapılmasına Dair Kanun, 2013). International students must register for General Health Insurance within three months of enrolling at their university, through the Social Security Directorates or affiliated Social Security

Centers located in the city where their university is based. After obtaining their foreign identity number within these three months, international students can apply online via the e-Government portal. Once the residence permit card is received, the following steps must be followed for the General Health Insurance application: The YU (Foreign Student) number should be reported to the International Student Office for updating records; students must visit the nearest PTT branch to obtain an e-Government password; log in to [http://www.turkiye.gov.tr]; use the search bar to find the service titled "Foreign Students – GSS [General Health Insurance] Application and Tracking", click on "new application", and submit the application; after a few days, revisit the same page to confirm the application approval; then, by logging into [https://www.turkiye.gov.tr/sosyal-guvenlik-sosyal-guvenlik-kurumu-kart-ile-prim-odeme-uygulamasi] with the e-Government password, select "Other Collections – GSS [General Health Insurance] Premium", enter the "YU number" starting with 99, and make the payment; after completing the payment, within a maximum of thirty days, obtain the eligibility document from [https://www.turkiye.gov.tr/spas-mustahaklik-sorgulama]; finally, this document should be submitted to the relevant Provincial Migration Management document unit with a petition, without the need to schedule an appointment. International students who fail to complete their application within the specified period will not be able to benefit from the General Health Insurance provisions during their studies. The only exception is that students who change their department/program or educational level regain the right to apply for General Health Insurance (Baş & Eti, 2020).

The obligation for international students to register with the Republic of Türkiye Ministry of Interior Presidency of Migration Management is important in determining the scope of health services they can benefit from according to their legal status. The advantages provided by health insurance for international students include access to hospital services, discounted prices for examinations and treatments, and quick access in emergencies. These regulations facilitate the higher education process in Türkiye and enhance the health security of international students.

In addition to the insurance-based system, practical aspects of direct health service delivery also shape the experiences of international students. Emergency

health services are among the most critical needs of international students in Türkiye. State hospitals and university hospitals in Türkiye provide emergency health services to international students. The Ministry of Health has developed various practices and regulations to facilitate access to these services. Rapid access to healthcare in emergencies is crucial to prevent negative impacts on students' educational processes. Moreover, the quality and accessibility of health services directly affect the experiences of international students in Türkiye. The efforts of the Ministry of Health aim to provide a safe environment for students (SGK, 2014). However, the lack of communication in foreign languages and limited cultural awareness of healthcare personnel reduce the quality of access to emergency services and hinder effective use of these services.

In addition to the structural challenges related to emergency health services, the content and scope of information activities emerge as another critical factor. Another important effort by the Ministry of Health aimed at international students is to provide information about their health rights and access to health services. These information activities aim to educate students about how the health system operates, insurance procedures, and ways to access health services. Such informational efforts help students understand the health system and manage potential health issues. The Ministry of Health conducts these informational activities in cooperation with universities and organizes seminars for students. These seminars facilitate the integration of students into the local health system and positively impact their access to health services (SGK, 2014).

On the other hand, some universities and healthcare institutions organize health screening programs to assess the health status of international students. These programs are designed to identify students' health conditions at an early stage and provide necessary health services. Health screening programs play a critical role in ensuring students have a healthy educational experience. Such practices minimize students' health concerns and allow them to focus on their education (SGK, 2014). However, these information activities are generally conducted only in Turkish, are not implemented within a systematic program, and show significant variation between universities. Students often struggle to exercise their rights because they do not know which health institutions to apply to, or which services are covered. To address these shortcomings, the system must be evaluated as part of a comprehensive integration process.

The integration of international students into the local health system is another important project carried out by the Ministry of Health. These projects facilitate easier access for students to health services in Türkiye and support their social integration. The Ministry of Health develops various strategies aimed at shaping the local health system according to the needs of international students. These strategies simplify the processes through which students benefit from health services and enhance their adaptation to social life (SGK, 2014).

However, the Ministry of Health's 2024–2028 Strategic Plan does not include a direct objective specifically dedicated to international students. The absence of visibility for this group in strategic documents regarding their right to health creates a policy gap in their access to health services (Republic of Türkiye Ministry of Health, 2023). Additionally, some students experience uncertainty about inclusion in General Health Insurance system due to incompatibilities between their home countries' insurance systems and Turkish regulations. Variations in the practices of university international student offices can lead to unequal access issues. Addressing these structural and implementation-related problems requires strengthening the legal framework as a priority.

The Ministry of Health adopts a comprehensive approach to protect the health rights of international students and facilitate their access to health services. Efforts such as mandatory health insurance, access to emergency health services, information campaigns, health screening programs, and integration into the local health system form the foundation of this initiative. These efforts aim to enhance the health security of international students studying in Türkiye and improve their educational experience. The policies implemented by the Ministry of Health play a significant role in increasing the quality of life for international students in Türkiye (SGK, 2014).

Legal regulations regarding health insurance for international students studying in Türkiye facilitate their access to health services and reduce uncertainties during this process. Health insurance is critically important both for the students and the sustainability of the health system. Therefore, the regulations designed to ensure the health security of international students positively affect their educational lives. Access to health services improves students' overall quality of life, making their educational processes more efficient. This, in turn, positively

impacts their academic success. Moreover, health security makes international students' experiences in Türkiye more positive, which leads them to share better impressions about Türkiye when they return to their home countries. From another perspective, international students not only contribute economically to the country but also offer cultural richness. This interaction strengthens Türkiye's international image and plays an important role in cultural diplomacy.

DISCUSSION AND CONCLUSIONS

This study evaluated the right of international students studying in Türkiye to access health services from the perspective of normative legal regulations and administrative practices. The constitutional guarantee of the right to health in the relevant articles of the Constitution of the Republic of Türkiye and in international human rights treaties demonstrates that the legal infrastructure of this right is strong. Constitutional Court of the Republic of Türkiye interpretations, which clarify that the concept of "everyone" in the Constitution is not limited to citizens but includes all individuals within Türkiye, show that international students' right to health is constitutionally protected. However, it is a clear reality that this normative infrastructure is not applied equally and effectively in practice, with barriers such as language difficulties, bureaucratic complexity, and lack of information limiting access to health services. This situation reveals a significant gap between constitutional guarantees and administrative practices. In particular, difficulties in accessing the health insurance system pose a serious obstacle to international students benefiting equally from health services. The complexity of health insurance applications, bureaucratic hurdles encountered during General Health Insurance applications, combined with language and cultural barriers, make it difficult for students to understand and manage the process. For example, many students fail to complete the required documents correctly or fail to comply with deadlines during the insurance application process. This has negative consequences for both academic success and health security. On the other hand, a lack of coordination between universities, SGK, and Ministry of Health causes the process to vary between universities and provinces, increasing inequalities in access. Despite Türkiye's internationalization policies claiming inclusivity, these practices hinder international students from equally benefiting from their right to health and lead to individual grievances.

The insufficient foreign language skills and lack of cultural awareness among healthcare personnel reduce the quality of health services, and communication problems—especially in emergency healthcare—directly threaten the quality of life and health safety of international students. At this point, it becomes essential to expand training programs aimed at increasing cultural sensitivity within healthcare institutions, and to establish translation services and intercultural communication units. On a case-by-case basis, many international students visiting emergency departments are unable to express themselves accurately, which can lead to treatment delays and misdiagnoses. Therefore, establishing professional support mechanisms in this area will improve both the accessibility and quality of health services.

Lack of information forms the basis of access problems, as international students often do not have sufficient knowledge about how the healthcare system operates, their rights, and health insurance processes, resulting in their inability to utilize these rights. Existing information sessions are generally conducted in Turkish, and there are significant differences in practices among universities. For example, some universities organize seminars on health rights and insurance, while others have no such programs. This inequality creates disparities among students and leads to injustices in access to health services. The absence of specific targets for international students in the Ministry of Health's strategic plans indicates that this deficiency is a structural problem.

The change between Law No. 5978, which defines the legal status of international students in Türkiye, and the former regulation under Law No. 2922, represents a significant development in enhancing the coordination of health services and improving the effectiveness of services provided to international students. However, the current legal framework remains insufficient in the face of rapidly increasing student numbers and evolving needs. Legal regulations need to be adjusted and updated regarding the inclusion of students in health insurance coverage, determination of insurance premiums, and expansion of coverage.

Moreover, for students coming from countries with social security agreements with Türkiye to have their insurance recognized domestically, the processes must be made more transparent and accessible. Strengthening international cooperation and diplomatic relations is also crucial in this regard.

The direct provision of health services and the quality of these services constitute another challenge in practice. Although emergency health services offered at state and university hospitals are accessible, the quality of these services remains limited due to healthcare personnel lacking sufficient multilingual and cultural competencies. To facilitate early detection of students' health issues and prompt referral to treatment, health screening programs should be expanded in universities. These programs would support students' academic success and enhance their quality of life in Türkiye. For example, health screening programs piloted at some universities have provided significant benefits by enabling early detection of chronic illnesses among students; however, these initiatives have not been widely implemented. In this context, the proposed solutions require a multidimensional and integrated approach.

The preparation of multilingual guidance and informational materials related to the health insurance application process, as well as strengthening the coordination between international student offices and social security and health institutions, should be the initial steps. Professional training and interpretation services should be provided in healthcare institutions to increase cultural awareness and language support, and these supports should be made mandatory in emergency health services. The Ministry of Health should set specific targets for international students in its strategic plans, strengthen data collection mechanisms, and regularly analyze the types and prevalence of barriers. Universities should expand health screening programs to regularly monitor students' health conditions and facilitate early intervention.

Meanwhile, the scope of social security agreements that Türkiye has signed with other countries should be expanded, and processes simplified. The experiences of international students should be regularly collected and taken into account in policy development processes. Participatory and rights-based approaches will improve the quality of health services while ensuring equal access to these services.

In conclusion, the rapid increase in the number of international students in Türkiye has made it necessary to develop inclusive, accessible, and equitable policies not only in education but also in health services. Despite a strong normative legal infrastructure, language barriers, bureaucracy, and lack of information in practice prevent the full exercise of the right to health.

Addressing these issues will enhance international students' academic success and quality of life, strengthen Türkiye's prestige in international education, and contribute significantly to social cohesion and cultural diplomacy. Thus, international students will be secured not only during their educational journey but also in terms of their health rights and overall quality of life, making their experience of studying in Türkiye more meaningful and positive.

Ethical Approval: This study does not require ethical approval, as it is based solely on the analysis of publicly available documents and does not involve human participants or personal data.

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Pharmaceutical Market Access in Türkiye: Processes, Challenges, and Opportunities

Öznur SEYHUN[1]

ABSTRACT

The primary objective of this study is to provide an analysis of pharmaceutical market access processes in Türkiye by examining approval, pricing, reimbursement, and entry barriers. It addresses the roles of the Turkish Medicines and Medical Devices Agency (TİTCK) and the Social Security Institution (SGK) in access to medicines, presents recommendations for solutions to encountered challenges. Access to pharmaceuticals in Türkiye involves a multi-stage and challenging process, including approval, pricing, and reimbursement steps. Key obstacles include bureaucratic delays, a lack of transparency in pricing processes, and the complexity of reimbursement procedures. Additionally, incentives for local production, alternative reimbursement agreements, and early access programs present significant opportunities to overcome existing limitations. It is crucial for pharmaceutical companies to understand Türkiye's regulatory framework and develop strategic plans. Policymakers might also consider reforms to improve transparency and expedite processes. Such improvements could lead to expansion in Türkiye's pharmaceutical market, quicker patient access to innovative treatments, increased local production, and enhanced independence. This study concludes that if the proposed recommendations are considered, Türkiye's regulatory and reimbursement policies can facilitate faster market access for new drugs, making the Turkish pharmaceutical sector more attractive to both local and global companies.

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Keywords: Drug Pricing, Emerging Markets, Health Policy, Market Access, Reimbursement

INTRODUCTION

Pharmaceutical market access is a multi-stage process involving approval, pricing, inclusion in the reimbursement list, and making a drug accessible to patients. This process includes a structure strategically managed by pharmaceutical companies and overseen by regulatory authorities. In developed countries, market access processes are generally more transparent and structured, whereas in emerging countries, these processes are more complex and fraught with various barriers (Koçkaya & Wertheimer, 2016).

Pharmaceutical companies typically base their pricing strategies on cost-effectiveness analyses and budget impact models in developed markets. Due to higher income levels and regulatory transparency, these markets provide faster access to medicines. In contrast, in emerging markets, particularly in countries like Türkiye, pharmaceutical companies face obstacles such as complex legal regulations, non-transparent pricing processes, and uncertainties in reimbursement mechanisms. Pharmaceutical market access in Türkiye is regulated and overseen by critical stakeholders, such as the Ministry of Health and the Social Security Institution (SGK). The Turkish Medicines and Medical Devices Agency (TİTCK) is responsible for licensing drugs, while SGK makes reimbursement decisions. However, as in other developing countries, the challenges pharmaceutical companies face in this process in Türkiye can prolong market entry times and limit patients' access to innovative drugs (Koçkaya & Wertheimer, 2016).

This study aims to detail the pharmaceutical market access processes, challenges, existing opportunities, and areas for improvement in Türkiye. Additionally, by highlighting the differences between developed and emerging markets, Türkiye's position within these processes will be better understood.

Pharmaceutical Market Access Process in Türkiye

Pharmaceutical market access in Türkiye is conducted within a framework established by regulatory authorities and through a rigorous inspection process coordinated by institutions such as TİTCK and SGK. The method of

making drugs available in the market includes the steps of licensing, pricing, and reimbursement.

Licensing

The first step in the pharmaceutical market access process is licensing. In Türkiye, drug licensing complies with international standards, such as those of the European Medicines Agency (EMA). Initially, TİTCK conducts Good Manufacturing Practices (GMP) inspections at production facilities for both local and imported products, ensuring the quality and safety of these products. Pharmaceutical companies prepare files in the Common Technical Document (CTD) format and submit them to TİTCK during licensing. These files contain detailed information about the drugs' effectiveness, safety, quality, and manufacturing.

License applications to TİTCK are evaluated and concluded within an average of 210 days following the GMP inspection processes, according to regulations in Türkiye. After GMP inspections and file reviews for drug production facilities, licenses are issued for approved products. However, this process can take longer due to complex bureaucratic steps and a lack of transparency (TİTCK, 2021; SGK, 2024; IQVIA, 2024).

Pricing

The drug pricing system in Türkiye is determined by the International Reference Pricing (IRP) method (Econix, 2024). This method is based on the prices of five central reference countries: France, Italy, Spain, Portugal, and Greece. If the drug has no cost in these countries, the prices of EU countries and PIC/S member countries are considered. Türkiye bases its drug prices on the lowest prices from the reference countries (Econix, 2024). According to the 2024 report by ECONiX, Greece, France, and Italy ranked as Türkiye's top three reference countries in 2023. The same report shows that apart from the five official reference countries, Germany and Switzerland are also referenced for original and generic products (Econix, 2024).

While TİTCK fixes drug prices through this reference pricing system, it also applies a fixed exchange rate to control currency fluctuations. The fixed exchange rate policy is implemented by assigning 60% of the previous year's

average Euro/TL rate as the fixed drug rate for the following year (TİTCK, 2021). The pricing system offers a mechanism to balance access to medicines for the public and private sectors. However, pharmaceutical companies indicate that this system creates pressure to lower drug prices, negatively impacting their profit margins (Econix, 2024). Under Decision No. 9063, published in the Official Gazette in 2024, the value of 1 Euro in Turkish Lira increased by 23.5% in October 2024 to a new periodic Euro value of 21.6721 TL (Republic of Türkiye Legal Gazette, 2024).

Studies have shown that lowering the Euro rate in drug pricing adversely affects access to medicines. When a system based on reference pricing models in Europe is applied, the low exchange rate makes economic sustainability in the drug supply chain more challenging, which can cause disruptions, especially in the supply of imported drugs (Organization for Economic Co-operation and Development [OECD], 2021). Additionally, the low Euro rate limits the ability of pharmaceutical companies to introduce innovative and high-cost treatments in markets like Türkiye, further restricting patient access (World Health Organization [WHO], 2018).

Reimbursement Process

Once the drug licensing and pricing procedures are completed, pharmaceutical companies apply to SGK for reimbursement. In this process, pharmaceutical companies must present cost-effectiveness and budget impact analyses. Including drugs in the reimbursement list requires a detailed examination of medical and economic data (IQVIA, 2024).

The Medical and Economic Evaluation Committee (TEDK), formed by SGK, reviews these files to determine the clinical and cost-effectiveness of drugs. TEDK's decisions are submitted to the Reimbursement Committee, and upon final approval, drugs are included in the reimbursement list under the Health Practices Communiqué (SUT) and published in the Official Gazette (IQVIA, 2024).

Challenges in Pharmaceutical Market Access

Complexity of Legal Regulations

Accessing Türkiye's pharmaceutical market requires coordination between institutions such as TİTCK and SGK. However, the lack of transparency and the

bureaucratic steps in these processes can make it difficult for pharmaceutical companies to complete them quickly. Especially in reimbursement applications, preparing and reviewing files can take a long time, becoming both costly and time-consuming for companies (IQVIA, 2024).

Pricing, Mandatory Discounts, and Control of Drug Expenditures

The drug pricing system in Türkiye creates significant price pressure for global pharmaceutical companies. In addition to the fixed 40% discount at the outset of pricing, a 41% public institution discount for original drugs and a 28% discount for generic drugs are applied. These rates can be incredibly restrictive for high-cost or innovative medications in terms of pricing. Consequently, some companies may hesitate to enter the Turkish market or face delays (Econix, 2024).

For 2023, SGK's budget was set at 537 billion TL, with 175.9 billion TL was allocated for drugs, and the remaining 361.1 billion TL was intended for other healthcare services. However, it was observed that the annual budget spent on drugs was 205.3 billion TL (an additional 29.4 billion TL), while 207.2 billion TL was spent on healthcare services (153.9 billion TL less than planned). Drug expenditures accounted for approximately 50% of the budget (Econix, 2024).

In 2022, total healthcare spending amounted to about 607 billion TL, with 76.4% covered by the government and 23.6% by the private sector. Total healthcare expenditure as a percentage of GDP decreased from 4.9% in 2021 to 4% in 2022. The ratio of current healthcare spending to GDP was 4.6% in 2021 and 3.7% in 2022 (Turkish Statistical Institute [TURKSTAT], 2023). As the share of total healthcare spending has declined in recent years, the share of healthcare spending within Türkiye's central budget is also lower than in other sectors. For example, in the 2024 Central Government Budget, 732.5 billion TL was allocated to the Ministry of Health, while 1.092 trillion TL was allocated to the Ministry of National Education. Given discussions about increasing the budget allocated to education to create a healthy society and an educated future generation, it becomes essential to use resources efficiently and allocate them according to proper priorities. This raises questions about the relatively high share (around 50%) of drug expenditures within the overall budget.

Another key topic of recent discussions has been the income-expenditure balance of SGK. It has been emphasized that SGK's income has not been sufficient to cover its expenditures, resulting in a continual deficit. However, analyzing the reasons for this deficit according to specific insurance branches would be a more accurate approach. For instance, in 2023, General Health Insurance premium income was 520.4 billion TL, while SGK's actual expenditure was 412.5 billion TL, resulting in a budget surplus of 107.9 billion TL for General Health Insurance in 2023. This surplus is not unique to 2023; in 2021, there was a budget surplus of 13 billion TL between GHI premium income and expenditures, and in 2022, a surplus of 42 billion TL was recorded. In 2023, this surplus reached 107 billion TL. These figures indicate that SGK's deficits are not due to healthcare expenditures but rather the costs associated with other insurance branches. This reality suggests flexibility regarding the potential for increased healthcare spending (Presidency of Türkiye, Presidency of Strategy and Budget, 2023).

Length of the Reimbursement Process

It can take an average of three years from the initial license application for a drug to be included in the reimbursement list. This process causes significant delays in making drugs available in the market and limits access to innovative treatments. Moreover, the detailed preparation of cost-effectiveness analyses and budget impact analyses requested by SGK can further prolong these processes (Costello Medical Consulting Ltd., 2017; IQVIA, 2024).

The European Federation of Pharmaceutical Industries and Associations (EFPIA) 2023 Waiting to Access Innovative Therapies (WAIT) report highlights significant differences in wait times for new drugs to reach the market following approval, comparing European access times. The report shows the average waiting period (i.e., the time between a drug receiving authorization from the European Medicines Agency (EMA) and its introduction to national markets) and the number of new medications available.

The report lists Germany, Denmark, and Switzerland among the countries with the shortest waiting times for access to new drugs, generally making drugs available within 120 days after approval. However, in Western European countries such as Spain and Italy, this period ranges from 250 to 350 days, with

delays due to additional bureaucratic processes and national reimbursement procedures (Newton et. al., 2024a).

On the other hand, Eastern European countries (e.g., Romania and Bulgaria) show significantly longer waiting periods, typically exceeding 600 days and sometimes taking several years. These delays are attributed to challenges in price negotiations, limited healthcare budgets, and more complex approval processes (Newton et. al., 2024a).

The report also notes that Sweden and the Netherlands have shorter-than-average waiting periods, as transparent and efficient drug evaluation processes characterize their national healthcare systems. Countries like Poland and the Czech Republic are at average levels in terms of waiting time, indicating a need for policy reforms to expedite their drug access processes (Newton et. al., 2024a).

These findings reveal that health inequalities in access to medicines have significant implications for patients and healthcare systems, underscoring the need to address these disparities through improved healthcare policies (Newton et. al., 2024a).

The EFPIA 2023 WAIT report also provides data on total accessibility by approval year (2019-2022). According to the report, drugs approved between 2020 and 2022 were accessible immediately in fewer countries. This situation occurred when the COVID-19 pandemic and economic restrictions strained health systems. Countries such as Germany and Denmark were among those with high accessibility rates, and quickly brought approved drugs to market. In these countries, most drugs approved after 2020 became accessible within 6-12 months.

On the other hand, Eastern European countries (e.g., Romania, Bulgaria, and Slovakia) exhibited lower accessibility rates based on the approval date, with drug market entry typically taking 2 to 3 years or longer. Low accessibility in these countries is attributed to limited healthcare budgets, challenges in price negotiations, and bureaucratic reimbursement procedures (Newton et. al., 2024a).

France and Italy have also shown fluctuations in inaccessibility based on the approval date. Particularly after 2020, the period between drug approval and market availability in these countries remained between 18 and 24 months, mainly due to the complexity of national evaluation and reimbursement processes (Newton et. al., 2024a).

Additionally, certain Northern and Western European countries like Sweden, the Netherlands, and Belgium demonstrated above-average speeds in providing access to approved drugs. These countries typically brought new drugs to market within one year of approval, ensuring patients timely access to innovative treatments (Newton et. al., 2024a).

In summary, the significant variation in accessibility by approval date across different regions in Europe is due to differences in healthcare policies, budget constraints, and regulatory processes. The report suggests that these disparities necessitate a review of national healthcare policies and drug evaluation processes, recommending strategic solutions to reduce inequalities in drug access (Newton et. al., 2024b). When examining accessible product breakdowns, five out of six innovative products in Türkiye are licensed and included in the public reimbursement list. However, one product with restricted access is not licensed, and patients access it via the Overseas Drug List. Although 10% of 167 innovative drugs in Türkiye are not publicly reimbursed, they are accessible through out-of-pocket payments. Previous WAIT surveys indicate that access to innovative treatments in Türkiye was measured at 20% in 2018, but this rate has declined yearly, placing Türkiye at lower ranks among the surveyed countries (Newton et. al., 2024a).

In particular, Türkiye's access rate, which showed a sharp drop to 6% in 2022, fell further to 4% in 2023. In the "Access to Innovative Treatments in Türkiye" section of the WAIT report, detailed data is presented on access rates to innovative orphan drugs approved by EMA between 2019 and 2022 across various countries. During this period, 63 orphan drugs received EMA approval. Among these, only one drug was accessible through public reimbursement in Türkiye in 2023, and it was accessible with limited access through the Overseas Drug List. Compared to other countries, access to orphan drugs in Türkiye is reported to be highly limited (IQVIA, 2024).

Access to medications for rare diseases is a significant issue for patients and the healthcare system. The drugs used in treating these diseases are generally high-cost, and many patients are unable to access needed treatments due to accessibility issues. A study by Sciascia et al. (2023) draws attention to the difficulties of accessing medications for rare diseases. The study findings indicate that delays in treating rare diseases negatively impact patients' quality

of life and require sustainable solutions within the healthcare system. In this context, developing a more comprehensive strategy to improve access to medications for rare diseases is crucial.

Barriers to Access to Orphan Drugs

Access to orphan drugs in Türkiye faces significant challenges due to cost, regulatory hurdles, and limited reimbursement (Alanay & Özbek, 2019). According to the analysis, only 71 out of 105 orphan drugs listed by the European Medicines Agency (EMA) are accessible in Türkiye. Of these, a mere 23 drugs (32%) are licensed, while the remaining 48 (68%) are unlicensed and often require off-label approval processes. This delays availability and imposes additional administrative burdens on physicians and patients (Koçkaya et. al., 2021).

Reimbursement is another critical barrier. Among the 71 accessible drugs, only 34 (48%) are covered by reimbursement. Notably, 17 licensed products (74%) are reimbursed, compared to just 17 unlicensed ones (35%). Patients often face high out-of-pocket expenses for drugs not covered by reimbursement. For example, the average cost of orphan drugs in Türkiye increased from €1,554.21 in 2017 to €3,907.32 in 2019. This rise is partly attributed to the inclusion of high-cost drugs like nusinersen, which is priced at €90,000 per unit (Koçkaya et al., 2021).

These barriers highlight the urgent need for updated national policies and better collaboration between pharmaceutical companies and policymakers to improve affordability and accessibility for patients with rare diseases.

Decrease in Public Health Expenditures

Between 2002 and 2019, Türkiye experienced a notable decline in healthcare expenditures as a percentage of GDP, reflecting shifting national priorities and economic strategies. In 2002, healthcare expenditures accounted for 5.2% of the GDP, but by 2019, this figure had decreased to 4.7%. This trend contrasts with global developments, where healthcare spending generally rises due to factors such as technological advancements and aging populations (Doğuç, 2021).

The decline in Türkiye's healthcare spending is attributed to multiple factors, including structural adjustments and efforts to optimize the allocation

of public resources. Despite this reduction, healthcare needs, driven by an increasing burden of chronic diseases and an aging population, continue to grow. As a result, policymakers face challenges in maintaining access to quality healthcare while addressing financial constraints within the public health system (Doğuç, 2021).

Cultural Barriers and Public Attitudes

Cultural and social attitudes significantly influence public health initiatives, including vaccination programs. In Türkiye, vaccine hesitancy and outright rejection have increased in recent years, with the number of families refusing vaccination surpassing 20,000 by 2018. This hesitancy often stems from deeply rooted cultural and personal beliefs, misinformation, and distrust in medical authorities. For instance, some parents cite religious or philosophical reasons for refusing vaccines, while others express concerns about vaccine safety and side effects despite extensive scientific evidence to the contrary (Yüksel & Topuzoğlu, 2019).

Research highlights that parental attitudes toward vaccination are shaped by various factors, including perceived risks, trust in healthcare providers, and exposure to anti-vaccination messages. In high socioeconomic groups, vaccine hesitancy is more prevalent, driven by fears of societal judgment and misinformation found on digital platforms. Notably, the dissemination of unscientific claims, often amplified through social media and influential public figures, has exacerbated public doubts (Yüksel & Topuzoğlu, 2019).

The challenges posed by vaccine hesitancy serve as a broader example of how cultural barriers and public attitudes can impact the acceptance of other medical treatments and innovations. For instance, reluctance toward new therapies, including gene therapies, advanced biologics, or even routine screenings, often mirrors similar patterns of misinformation and distrust. Addressing these issues requires a multi-pronged strategy: engaging trusted community leaders, promoting health literacy, and countering misinformation through targeted evidence-based communication. By learning from vaccination efforts, policymakers can develop frameworks to anticipate and mitigate resistance to other essential treatments, ensuring equitable access and public trust across the healthcare spectrum.

Opportunities and Areas for Improvement

Incentives for Local Production

Türkiye aims to reduce its dependency on drug imports by promoting local production, creating employment, and enabling technology transfer. The incentives offered to local manufacturers give them priority in licensing and pricing processes. Public institution discount rates for locally produced products are also more favorable. This approach enhances the competitive power of local pharmaceutical companies in Türkiye, contributing to the country's goal of self-sufficiency in the pharmaceutical sector (TİTCK, 2024; Econix, 2024). Companies producing locally can request differentiated prices by providing rationales with cost cards independent of the reference price.

There is a need for more skilled researchers and increased technical capacity in drug development. This figure falls below the OECD average. Relative to Türkiye's R&D potential, the number of centers of excellence for clinical and preclinical development is also insufficient. Although the number of researchers remains low compared to the global knowledge pool, it is increasing rapidly in countries like Türkiye. Between 2008 and 2016, the number of researchers in Türkiye grew by 62%, likely to continue with the country's increasing financial investments in R&D (UNESCO Institute for Statistics, 2019).

Alternative Reimbursement Agreements

Türkiye offers Alternative Reimbursement Agreements (AGÖK), especially for high-cost and innovative drugs. These agreements include flexible models such as risk-sharing, performance-based reimbursement, and budget constraints. Such agreements enable innovative treatments to be introduced more quickly and effectively. For instance, a high-cost oncology drug can be included in the reimbursement list within a deal with SGK based on clinical outcomes or performance data (Koçkaya et al., 2021).

Early Access Programs for Innovative Drugs

Türkiye has programs such as the "Humanitarian Early Access Program" and "Overseas Drug Supply", which allow patients access to innovative treatments earlier in critical situations. Through these programs, pharmaceutical companies can introduce their products to the market before clinical trials

are completed, increasing patient access and strengthening the company's positioning in the Turkish market (Vural et al., 2012; Koçkaya et al., 2021).

Overseas Drug

Patients in Türkiye can access drugs that have not yet received marketing authorization approval or are not included in the reimbursement list through the Patient-Based Drug Sale program. This includes orphan drugs used for rare diseases. These drugs are imported by TİTCK with special approval based on individual patient evaluations.

Digital Health Technologies

Digital health technologies are transforming healthcare, offering opportunities to enhance patient care and streamline clinical workflows. Tools such as wearable sensors enable continuous monitoring, providing real-time data for accurate diagnoses and personalized treatment plans. 3D printing offers innovative solutions in precision medicine by producing customized drug dosages tailored to individual patient needs, particularly for diseases with variable treatment responses. Similarly, robotics and IoT technologies improve efficiency, from enabling minimally invasive surgeries to delivering essential medical supplies in remote areas via drones. These advancements also promise cost reduction and scalability, which are vital for addressing the growing demands on healthcare systems (Awad et al., 2021).

However, challenges remain in integrating these technologies into existing healthcare infrastructures. Data security and privacy concerns are significant, particularly with IoT-connected devices handling sensitive patient information. Additionally, high costs may limit access for low-income populations, exacerbating health inequities. Ethical considerations, including the potential displacement of healthcare jobs by automation, further highlight the need for balanced adoption. Addressing these challenges through robust regulations, equitable policies, and hybrid human-digital models will ensure the full potential of digital health technologies can be realized, benefiting diverse populations globally (Awad et al., 2021).

Improvement in Supply Chain

Efficient supply chain management is pivotal for reducing costs and enhancing the quality of healthcare services. Despite its critical role, the healthcare supply chain lags behind its commercial counterparts in adopting advanced logistics tools and strategies. For instance, inventory turnover rates in healthcare average only 2 compared to 44 in consumer electronics, highlighting inefficiencies that contribute to higher operating costs. Logistics expenses alone account for 38% of healthcare costs, significantly more than industries like retail (5%) or electronics (2%) (Kwon et al., 2016).

Adopting advanced tools such as Vendor Management Inventory (VMI) and Collaborative Planning and Forecasting Replenishment (CPFR) could transform healthcare supply chains. VMI shifts inventory management responsibility to manufacturers, reducing errors and costs while improving service levels. Similarly, CPFR fosters collaboration between manufacturers and providers, optimizing inventory levels and ensuring the timely availability of critical supplies. By embracing such strategies, healthcare systems can reduce waste, lower costs, and reinvest savings into improving patient care and innovation (Kwon et al., 2016).

Efforts to improve supply chain processes, including standardization and lean management principles, are equally essential. Standardized processes eliminate redundancies, enhance transparency, and streamline operations. Lean management focuses on reducing waste across the supply chain, improving efficiency, and freeing up resources for critical healthcare needs. Together, these strategies can modernize the healthcare supply chain, ensuring better patient outcomes and more sustainable operations (Kwon et al., 2016).

CONCLUSION AND RECOMMENDATIONS

Access to the pharmaceutical market in Türkiye is a complex, multi-stage process. Each phase—licensing, pricing, and reimbursement—is a critical step that pharmaceutical companies must manage carefully. Despite the challenges associated with these processes, Türkiye offers numerous opportunities for growth and innovation in the pharmaceutical sector. Local production incentives and alternative reimbursement models are significant steps toward accelerating market entry and improving patient treatment access.

Supporting and encouraging local production can reduce Türkiye's dependency on pharmaceutical imports, thereby strengthening the economy. Additionally, SGK's risk-sharing and performance-based reimbursement models can accelerate market entry for innovative drugs, thereby advancing progress in the healthcare sector.

Improving transparency, reducing bureaucracy, and enhancing coordination among regulatory bodies can help alleviate the obstacles pharmaceutical companies face. These improvements can make Türkiye's pharmaceutical market more competitive and better aligned with international standards. As a result, pharmaceutical companies will be able to enter the Turkish market more quickly, providing patients with earlier access to innovative treatments.

Türkiye is focusing on investment incentives, technology transfer, digitalization in healthcare, and health tourism to attract additional foreign investment. Successful Public-Private Partnership (PPP) projects in Türkiye have led to improved health outcomes. Other countries in the region have the opportunity to replicate elements of government-private sector coalitions and technology exchange programs.

Improvements in the healthcare system can significantly help achieve the goals of various stakeholders. The Ministry of Health's efforts to expedite access to medicines should be evaluated within this context. Facilitating drug access can address unmet needs more rapidly and reach a broader patient base. These improvements enhance the effectiveness of healthcare services and improve patients' quality of life.

The findings of this study, based on industry reports and academic research, provide a solid foundation for the results. For instance, the Association of Research-Based Pharmaceutical Companies (AIFD) reports address the current state of access to medicines and necessary improvements. Additionally, studies on orphan diseases emphasize the importance of personalized healthcare by highlighting patients' distinct genetic and molecular needs (Alanay & Özbek, 2019). These kinds of reports and research offer valuable references for assessing the positive effects of strategic steps to accelerate access to medicines on public health.

Efforts by the Ministry of Health to improve access to medicines must be coordinated with other stakeholders in the sector. These efforts will speed up the resolution of patients' unmet needs and enhance access to healthcare

services. This approach will raise the overall efficiency of the healthcare system and maximize public health benefits.

Making pharmaceutical market access processes in Türkiye more efficient and transparent will help pharmaceutical companies enter the market more quickly, allowing patients to access innovative treatments sooner. The following actions can be taken to achieve this:

1. Enhance Transparency in Regulatory Processes: Institutions such as TİTCK and SGK need to conduct their processes more transparently and expedite them to facilitate the market access process for companies.

2. Strengthen Local Production and R&D Incentives: Providing more incentives for local production and innovative drug development processes in Türkiye will support the growth of the domestic pharmaceutical sector.

3. Expand Alternative Reimbursement Models: In particular, more risk-sharing and performance-based reimbursement models should be applied to high-cost drugs to accelerate the market entry of innovative treatments. Value-based reimbursement methods and practices should be closely monitored in this regard.

4. Leverage Digital Health Technologies in Market Access: Integrating digital health technologies, such as electronic health records and data analytics, can improve the evaluation of treatment outcomes and support performance-based reimbursement agreements. These tools enable more accurate and efficient assessments of innovative treatments, thereby facilitating faster market approvals and reimbursements.

5. Establish a Unified Stakeholder Engagement Framework: A centralized platform to engage stakeholders, including pharmaceutical companies, healthcare providers, patient advocacy groups, and regulators, can streamline discussions on pricing, reimbursement, and access challenges. Regular consultations with these groups will ensure that market access policies align with both industry needs and patient welfare, fostering collaboration and innovation.

In conclusion, making Türkiye's pharmaceutical market access processes more efficient presents significant opportunities for public health and the pharmaceutical sector. Taking advantage of these opportunities can position Türkiye as a stronger and more independent player in the pharmaceutical industry.

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Alzheimer's Disease: A New Paradigm, New Treatments, New Challenges, New Approaches

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia. Recent advances have shifted the focus from symptomatic treatments to early, disease-modifying strategies. This article reviews new therapeutic approaches, particularly monoclonal antibodies such as lecanemab and aducanumab, which aim to reduce amyloid-beta accumulation. Despite promising outcomes, safety concerns and high costs remain. Additionally, the development of biomarker-based diagnostic tools has led to ethical and clinical challenges in early detection. The article also highlights non-pharmacological interventions, such as multidomain lifestyle modifications, which may enhance cognitive reserve and delay disease onset. A public health framework is needed to integrate precision medicine, screening policies, and preventive strategies to address the increasing burden of Alzheimer's disease.

Keywords: Alzheimer's Disease, Biomarkers, Cognitive Reserve, Monoclonal Antibodies, Public Health

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INTRODUCTION

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder predominantly observed in the elderly population and represents the most common cause of dementia cases worldwide. The prevalence of AD increases with advancing age. Approximately 10% of individuals over the age of 65 and 35%-50% of those over the age of 85 are affected. In Türkiye, the average life expectancy is increasing (currently 78.3 years), and the proportion of elderly individuals is rising rapidly. While the population aged 65 and over was 7.5% in 2012, it reached 9.9% in 2023. This figure is projected to rise to 20.8% by 2050 and 27.7% by 2075 (Turkish Statistical Institute [TURKSTAT], 2024).

The pathophysiology of AD is characterized by abnormal protein aggregations, such as the accumulation of amyloid-beta (Aβ) plaques and the hyperphosphorylation of tau proteins. The interaction of these biological processes with neuroinflammation, oxidative stress, and synaptic dysfunction accelerates the neurodegenerative progression of the disease. However, the exact etiology of AD remains incompletely understood, and it is thought to arise from a complex interplay of multiple risk factors, including genetic components (e.g., the APOE ε4 allele), environmental influences, and aging (Jack et al., 2018).

Even in its earliest stages, AD dementia necessitates caregiving and imposes a significant burden on families, caregivers and healthcare systems. The magnitude of this burden increases in parallel with disease progression and symptom severity. Worsening cognitive impairment leads to greater loss of functional independence, increased demand for intensive care, and a growing societal burden. Therefore, slowing disease progression constitutes a critical goal for individuals with AD, their loved ones, and the healthcare system. At present, treatment primarily aims to slow disease progression.

In a study conducted by Chandler et al. (2024), it was shown that slowing disease progression by 20% in patients with early-stage AD could have meaningful effects on cognitive, functional, and behavioral outcomes. According to findings from the NACC database, slowing disease progression by 20% over five years in individuals with mild cognitive impairment (MCI) and mild dementia was associated with 1.7 points (10.8%) and 1.6 points (12.9%) less cognitive decline, respectively, in terms of the Systematic Symptom Score (SSS). The same intervention was also associated with approximately 20% less

behavioral deterioration in Neuropsychiatric Inventory (NPI-Q) scores, and it was reported to reduce the likelihood of becoming entirely dependent by 22.2% in the MCI group and 21.6% in the mild dementia group. According to ADNI data, slowing disease progression by 20% or 30% within four years contributed to reductions in cognitive decline by 20.4% and 29.6%, respectively.

These findings suggest that slowing the progression of early AD may enable patients to preserve their functional autonomy and quality of life for a more extended period (Chandler et al., 2024). Therefore, clinicians and policymakers must develop strategies to improve access to treatment during the early stages of the disease. Slowing disease progression in its early phase—preserving cognitive and functional abilities and maintaining relative independence—can benefit patients, their families, and society. This carries critical implications for patients, caregivers, clinicians, researchers, and policymakers (Desai et al., 2024).

The preclinical stage and early diagnosis have gained significant importance today due to the possibility of biological diagnosis through cerebrospinal fluid (CSF) and even blood samples, as well as the development of new-generation therapies aimed at clearing amyloid from the brain to slow the disease process. However, this emerging period has also introduced new ethical and societal challenges, along with the need for novel approaches that had not been previously discussed or fully recognized. This article aims to examine these issues and potential approaches related to this evolving landscape and to initiate a framework that may guide our country and policymakers.

New Therapeutic Approaches in Alzheimer's Disease (AD)

For nearly 25 years, treatment options for AD have been mainly limited to symptomatic management. However, recent intensive research efforts have focused on disease-modifying therapies, leading to several promising developments. Traditionally, acetylcholinesterase inhibitors (rivastigmine, donepezil, galantamine) and NMDA receptor antagonists (memantine) have served as standard treatments to alleviate mild to moderate symptoms of AD (Tan et al., 2014). While these medications were considered groundbreaking in the history of AD treatment, they are not effective in halting or slowing disease progression. Instead, they provide temporary relief from cognitive and behavioral symptoms.

In contrast, a new class of monoclonal antibodies targeting amyloid plaques has emerged as a promising type of disease-modifying therapy with the potential to slow disease progression. Alongside anti-amyloid antibody treatments, other emerging disease-modifying strategies are under development. These include tau-targeted therapies (e.g., tau antibodies and aggregation inhibitors), approaches modulating microglial activity through anti-inflammatory pathways, gene therapies, and several other investigational treatments (Cummings et al., 2024). It is hoped that these biological therapies—particularly when combined with early diagnosis—will enhance therapeutic efficacy and bring us closer to the goal of delaying disease progression. Nonetheless, further research and the development of novel strategies are needed to optimize the efficacy and safety of these interventions (Sevigny et al., 2016).

The following sections will briefly review these newly introduced therapeutic agents, which not only offer renewed hope but also raise novel questions regarding early and biological diagnosis.

Recent advances in treating AD have highlighted monoclonal antibodies (mAbs) as promising disease-modifying therapeutic agents. These therapies, approved by the U.S. Food and Drug Administration (FDA) (2023), specifically target β-amyloid (Aβ) plaques, a hallmark feature of AD. Two mAbs—aducanumab and lecanemab—have received FDA approval. While all monoclonal antibodies primarily aim to remove amyloid-beta plaques, they operate via different mechanisms.

Aducanumab targets fibrillar Aβ and oligomers with high affinity, while lecanemab preferentially binds to Aβ protofibrils, with a 10:1 selectivity ratio compared to plaque-bound Aβ. Donanemab recognizes a specific pyroglutamate-modified form of Aβ found exclusively in plaques.

Aducanumab was the first disease-modifying treatment approved by the FDA in 2021. It is indicated for early AD with confirmed Aβ pathology. Although efficacy data varied across Phase III trials, dose-dependent reductions in plaque burden and some cognitive benefits were observed.

Lecanemab received approval in 2023 for patients with mild cognitive impairment (MCI) or early-stage AD dementia. Phase II and III trials demonstrated significant plaque clearance and a slowing of cognitive decline,

with one trial reporting a 27% reduction. PET imaging confirmed plaque elimination in 81% of participants.

For both drugs, the most commonly reported adverse events were amyloid-related imaging abnormalities (ARIA), particularly cerebral edema (ARIA-E) and microhemorrhages (ARIA-H) (Van Dyck et al., 2023).

Currently, the most prominent and debated monoclonal antibody is lecanemab. In the study "Lecanemab in Early Alzheimer's Disease" by Van Dyck et al. (2023), lecanemab was estimated to provide a 27% clinical benefit in slowing AD progression. This 18-month, multicenter, double-blind Phase 3 trial enrolled participants aged 50 to 90 with early-stage AD characterized by mild cognitive impairment or mild AD dementia and confirmed amyloid pathology via PET imaging or cerebrospinal fluid (CSF) analysis.

In the lecanemab group, the most commonly reported adverse events (occurring in more than 10% of participants) included infusion-related reactions, cerebral microhemorrhages, macrohemorrhages, and superficial siderosis, along with ARIA-H (amyloid-related imaging abnormalities—hemorrhage), ARIA-E (amyloid-related imaging abnormalities—edema), headaches, and falls. These adverse events were predominantly asymptomatic, typically occurred within the first three months of treatment, and resolved in 81% of cases within four months (Van Dyck et al., 2023).

However, the FDA has reported deaths associated with ARIA-related edema in patients receiving lecanemab, raising concerns about the drug's safety profile (Maki et al., 2025). Moreover, the risk of hemorrhagic complications has been shown to increase with age, with higher rates observed in the lecanemab group, whose mean age was 71.4 ± 7.9 years. A significant concern regarding lecanemab is the increased incidence of ARIA—particularly brain edema and hemorrhage—in patients carrying the APOE ε4 allele, a common genetic risk factor for AD (Martorana et al., 2025).

Additionally, some studies have questioned the claimed efficacy of lecanemab. For example, one study suggested that the therapeutic benefit is significantly lower in women and in APOE ε4 carriers, implying a possible genetic basis for reduced responsiveness. The author argues that these differences were not adequately discussed in the published article and that the efficacy data for lecanemab may have been overstated (Kurkinen, 2023).

Due to these findings, the efficacy and safety profile of lecanemab and similar monoclonal antibodies has not been universally accepted worldwide. While lecanemab (Leqembi) has been approved in countries such as the United States and Japan, it has faced resistance in Europe. European authorities have adopted a more skeptical stance for several reasons. The European Medicines Agency (EMA) initially rejected the marketing authorization for lecanemab. Although a subsequent application was accepted, the EMA concluded that the anticipated benefits of the drug did not outweigh the significant risks of adverse effects, particularly cerebral hemorrhage and edema.

Some experts argue that the observed improvements in disease progression are too modest to provide meaningful clinical benefit to patients, raising further questions about the drug's role in the treatment landscape (Martorana et al., 2025). Another major obstacle to global approval of lecanemab is its high cost. In the United States, the annual price of lecanemab is approximately $26,500. If similar pricing were applied in Europe, the annual treatment costs could reach €133 billion—exceeding half of Europe's total pharmaceutical expenditures.

Such unsustainable pricing and high economic burden may severely limit or completely preclude access to the drug, particularly in countries with constrained healthcare budgets. Furthermore, estimates of lecanemab's cost-effectiveness are based on the assumption that it delays disease progression by three years; however, the clinical trial data supporting this assumption are limited to an 18-month follow-up period (Jönsson et al., 2023).

Biological Diagnosis of Alzheimer's Disease (AD) and Emerging Biomarkers

Until recently, the clinical diagnosis of AD primarily relied on conventional diagnostic criteria, which allowed for classifications such as "possible" or "probable" AD. A definitive diagnosis required postmortem identification of β-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) in the brain (McKhann et al., 1984). However, recent advances in fluid biomarkers and neuroimaging have enabled the in vivo detection of AD pathology, leading to the development of new diagnostic criteria by the International Working Group (IWG) and the National Institute on Aging–Alzheimer's Association (NIA-AA). These guidelines redefined AD by introducing diagnostic categories for asymptomatic individuals

with biomarker evidence of pathology (Dubois et al., 2014; Jack et al., 2018).

Biological diagnostic frameworks such as the ATN model—evaluating amyloid plaques (A), tau pathology (T), and neurodegeneration (N)—enable more precise characterization of AD subtypes and disease stages. Understanding these subtypes and stages facilitates the use of therapies tailored to the disease's biological underpinnings (Almeida et al., 2024).

The role of biomarkers in the diagnosis of AD is becoming increasingly critical. Commonly used cerebrospinal fluid (CSF) biomarkers include low Aβ42 levels and elevated levels of phosphorylated tau (p-tau) and total tau (t-tau). In addition, new imaging techniques, particularly amyloid and tau PET scans, support in vivo diagnosis. A significant recent advancement is the ability to detect specific biomarkers—such as p-Tau217, Aβ42/40 ratio, and neurofilament light chain (NfL)—in blood, which is expected to greatly simplify the diagnostic process (Jack et al., 2024).

Moreover, biomarker algorithms enhanced by artificial intelligence, neuroimaging, and neuropsychological testing now enable the detection of AD pathology during the preclinical stage. These developments contribute to a deeper understanding of AD pathophysiology and offer new opportunities for designing early intervention strategies (Atri, 2019; Jack et al., 2018).

At this point, we observe a divergence between the NIA-AA and IWG groups regarding the diagnostic framework for AD, as reflected in the recently published guidelines. According to the 2024 IWG criteria, individuals who are biomarker-positive but cognitively normal cannot be diagnosed with AD. In contrast, the 2024 AA criteria allow for an AD diagnosis based solely on biomarker positivity, even in the absence of cognitive impairment (Jack et al., 2024).

In this context, the IWG recommends re-evaluating the "Revised AA Criteria (2024)" and proposes an alternative conceptual framework in which AD is defined as a clinical-biological entity intended for use in clinical settings (Dubois et al., 2014).

Another important question concerns whether initiating treatment after symptom onset is genuinely effective in halting disease progression, given that amyloid-β accumulation begins 20 to 30 years before clinical symptoms appear. Therefore, interventions targeting Alzheimer's pathology should ideally commence prior to dementia onset. Current recommendations for monoclonal antibody use align with this perspective. The National Institute on

Aging–Alzheimer's Association (NIA-AA) has even proposed that individuals who are biologically positive for AD—despite having no cognitive impairment—be considered as having AD and, thus, eligible for treatment (Jack et al., 2024).

As a logical consequence of this framework, one of the most critical determinants of prognosis and therapeutic efficacy in AD is the establishment of a time window for early diagnosis and intervention. Longitudinal multimodal biomarker studies have shown that the continuum of AD includes a long latent phase—referred to as preclinical AD—that begins decades before symptom onset. Treatment may offer the best opportunity to slow disease progression during this preclinical phase. Effective therapies initiated at this stage may delay or even prevent cognitive decline. The recent success of anti-amyloid immunotherapy trials in symptomatic AD has fueled enthusiasm for testing such strategies at the earliest possible stage (Rafii & Aisen, 2023).

At this juncture, one of the key questions we aim to address emerges once again—an issue for which definitive answers remain elusive: How many individuals with a biological diagnosis of AD progress to clinical Alzheimer's dementia? Moreover, should we initiate treatment in all biomarker-positive individuals, even without cognitive symptoms?

In a retrospective observational cohort study comparing survival rates and relative mortality risk across different stages of AD—including AD-related mild cognitive impairment (MCI) and Alzheimer's dementia—with cognitively normal individuals, it was found that the median survival time for participants who progressed to MCI due to AD or to Alzheimer's dementia ranged from 3 to 12 years, with shorter survival durations observed at more advanced stages of the disease. Greater disease severity was associated with higher mortality, particularly among younger individuals. For instance, in a 65-year-old patient, disease severity increased the risk of death more than in an 80-year-old patient.

Participants with AD-related MCI had a mortality risk comparable to cognitively normal individuals after adjusting for confounding factors. These findings suggest that preventing or delaying the progression of AD may contribute to lower mortality—and more importantly, such a benefit may be more pronounced in relatively younger individuals (Crowell et al., 2023).

Evidence also indicates that within 5 to 10 years following a diagnosis of AD-related MCI, approximately 30% to 50% of individuals progress to Alzheimer's

dementia. This rate is even higher—approximately 15% greater—among individuals with amnestic MCI (Angevaare et al., 2022).

On the other side of the coin, preclinical AD affects a significant portion of cognitively unimpaired older adults—individuals who, under the 2024 AA criteria, would be diagnosed with AD based on biological markers. Today, blood-based biomarkers can detect very early changes in the AD continuum with high accuracy. However, the key uncertainty lies in whether these individuals will ultimately progress to clinical dementia.

For instance, in a relatively short 18-month study, no significant differences were observed using assessments such as plasma phosphorylated tau (p-tau)181 levels, cognitive performance measures, and brain MRI volumetrics, including hippocampal volume and cortical thickness (Pais, 2023). In contrast, an 8-year longitudinal study by Chen et al. (2022) demonstrated that cognitive tests such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS13) and the Mini-Mental State Examination (MMSE), along with cerebrospinal fluid (CSF) and plasma p-tau181, CSF sTREM2, and brain volume measurements, could predict long-term cognitive decline.

Furthermore, lifetime risks of Alzheimer's dementia vary significantly by age, sex, and disease stage, whether preclinical or clinical. For example, a woman with amyloidosis only has an estimated lifetime risk of 8.4% at age 90 but 29.3% at age 65. Individuals under the age of 85 who present with mild cognitive impairment, amyloidosis, and neurodegeneration have a lifetime risk exceeding 50%. Consequently, most individuals with preclinical AD will not develop Alzheimer's dementia during their lifetimes (Brookmeyer & Abdalla, 2018).

This suggests that more parameters are needed to guide decisions regarding who should receive treatment. Lifetime risk estimations can aid in interpreting the clinical relevance of biomarker-based screening for AD (Brookmeyer & Abdalla, 2018). Overcoming the prevailing "confirmation bias" is essential to advance the diagnosis and treatment of AD and to move toward precision medicine with a more nuanced understanding of amyloid biomarkers (Souchet et al., 2023). These findings underscore the need to consider not only biomarkers like amyloid but also additional parameters—such as those reflecting brain compliance—in the evaluation of amyloid-positive individuals who have not yet developed dementia.

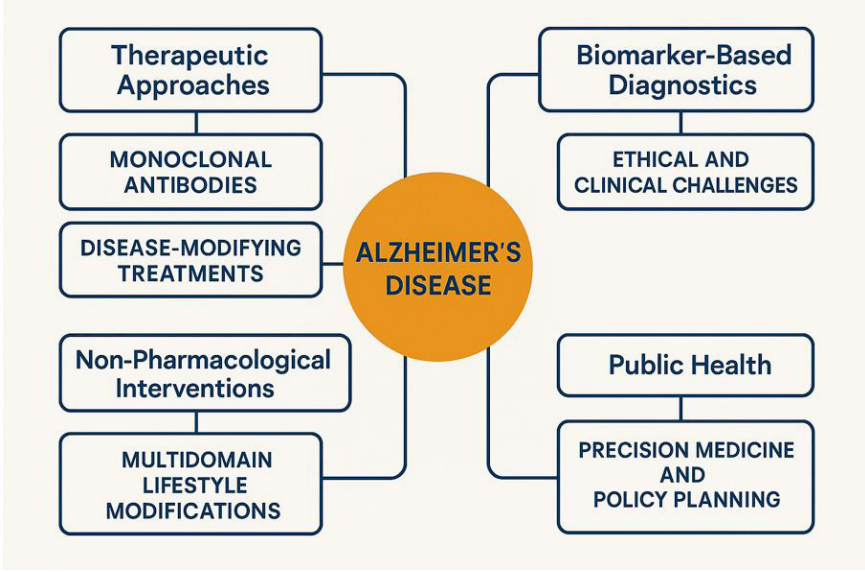

Figure 1. Multidimensional framework of Alzheimer's disease domains

The figure outlines therapeutic, diagnostic, and public health components of Alzheimer's disease, emphasizing the integration of clinical strategies with ethical and policy considerations.
Note. Created by the author.

In conclusion, emerging therapeutic approaches currently under development aim to target individuals at risk for AD prior to symptom onset or during the earliest stages when only mild signs are present. These developments pave the way for a system of primary prevention in which the general population—particularly individuals aged 50 and above—could undergo regular screening using plasma biomarkers. Such screening could detect disturbances in Aβ metabolism even before the accumulation of fibrillar amyloid in the brain begins, enabling the early identification of high-risk individuals (Gustavsson et al., 2021; Rafii & Aisen, 2023).

However, the models tested for such screenings are complex and remain inconclusive. Nevertheless, various strategies exist for identifying these individuals, including population-wide and tiered screening approaches. For example, the TRC-PAD (Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease) infrastructure describes a stepwise process to efficiently and cost-effectively screen a large population. This approach involves voluntary

online enrollment, web-based cognitive assessments, and subsequent plasma biomarker analysis for eligible candidates (Rafii & Aisen, 2023).

Each of these strategies, however, poses unique ethical challenges. To justify the ethical costs associated with current risk classification methods, the drugs developed must provide substantial health benefits to individuals identified as being at risk of developing AD. Evidence supporting such significant benefits from available drug candidates remains limited (Gustavsson et al., 2021).

Public Health Perspective and Non-Pharmacological Approaches

One approach that also offers a public health perspective involves non-pharmacological treatment strategies. Maki et al. from Japan—one of the countries where lecanemab has been approved for use—highlighted the drug's side effect profile and economic burden. They suggested that non-pharmacological interventions in individuals with MCI or AD may enhance cognition and cognitive reserve (CR), thereby helping individuals better resist the effects of AD pathology. Promoting social engagement in people with AD—such as participating in household chores, food service, or folding laundry, all of which involve reciprocal social interactions—may support cognitive reserve by engaging multiple cognitive domains. Even individuals over 90 with AD can actively participate in such roles. Furthermore, these interventions may potentially reduce the underlying AD pathology in the brain, including amyloid-β plaques and hyperphosphorylated tau proteins (Maki et al., 2025).

The SMARRT project (Supporting Multidomain Alzheimer's Risk Reduction Trial)—a randomized controlled trial evaluating the impact of personalized, multidomain interventions on reducing Alzheimer's risk—investigated how managing modifiable risk factors could influence the course of the disease. In this study, 172 individuals aged 70 to 89 who had at least two of the following eight modifiable risk factors were randomized into intervention and control groups: physical inactivity, uncontrolled hypertension, poor sleep quality, use of medications harmful to cognition, severe depressive symptoms, uncontrolled diabetes, social isolation, and smoking. The intervention group received individualized goals delivered with the support of a health coach and nurse (e.g., daily step counts, reading goals, sleep duration monitoring). In contrast, the control group received educational materials at regular intervals. After a two-

year follow-up period, cognitive function improved by more than 74% in the intervention group. This study highlighted the value of non-pharmacological treatments in reducing Alzheimer's risk and preserving cognitive function, especially considering their low cost and ease of implementation compared to drug-based treatments (Yaffe et al., 2024).

Indeed, the 2024 update of the Lancet Commission on Dementia emphasized the high potential for prevention, suggesting that nearly half of all dementia cases could theoretically be prevented by addressing 14 modifiable risk factors. These include physical inactivity, smoking, traumatic brain injury, depression, hearing loss, hypertension, high cholesterol, obesity, excessive alcohol consumption, social isolation, vision loss, air pollution, and—most notably—low educational attainment, which is closely linked to cognitive reserve (Livingston et al., 2024). Dementia risk reduction efforts should begin early and continue across the lifespan. Risk can be modified independently of APOE genetic status. Multicomponent interventions targeting multiple risk factors may offer substantial benefits for individuals at both high and low genetic risk for dementia. Even addressing a subset of these factors could yield meaningful benefits. For example, a modeling study in the United Kingdom estimated that treating hypertension, promoting smoking cessation, and providing hearing aids could reduce dementia prevalence by 8.5% and save the UK £1.86 billion annually (Livingston et al., 2024).

The Need for Change in National Aging and Dementia Policies

In conclusion, advances in biomarker-based diagnostics and the development of disease-modifying therapies such as lecanemab represent significant milestones in the fight against AD. However, challenges persist in achieving effective early intervention and personalized treatment strategies, as well as in addressing the multifactorial nature of the disease, which also gives rise to new ethical and societal concerns. Experts suggest that while amyloid-clearing therapies may address one aspect of Alzheimer's pathology, combination therapies targeting additional mechanisms of disease may be required in the future (Kwon, 2024).

A holistic approach that integrates novel biomarkers, combination therapies, lifestyle interventions, and a deeper understanding of AD pathophysiology will

improve patient outcomes and quality of life in the coming years. It increasingly appears that the transition from "biological AD" to clinical dementia is primarily determined by "cognitive reserve." Thus, there is an urgent need for population-level screening tools capable of accurately measuring this parameter.

Research funding and policy direction should shift from broad, nonspecific biomarker searches toward efforts focused on characterizing cognitive reserve and disease resilience. Identifying individual risk profiles—and the corresponding disease subtype—would enable tailored, person-specific interventions. Consequently, subtype-focused studies represent another critical area that requires prioritization and support.

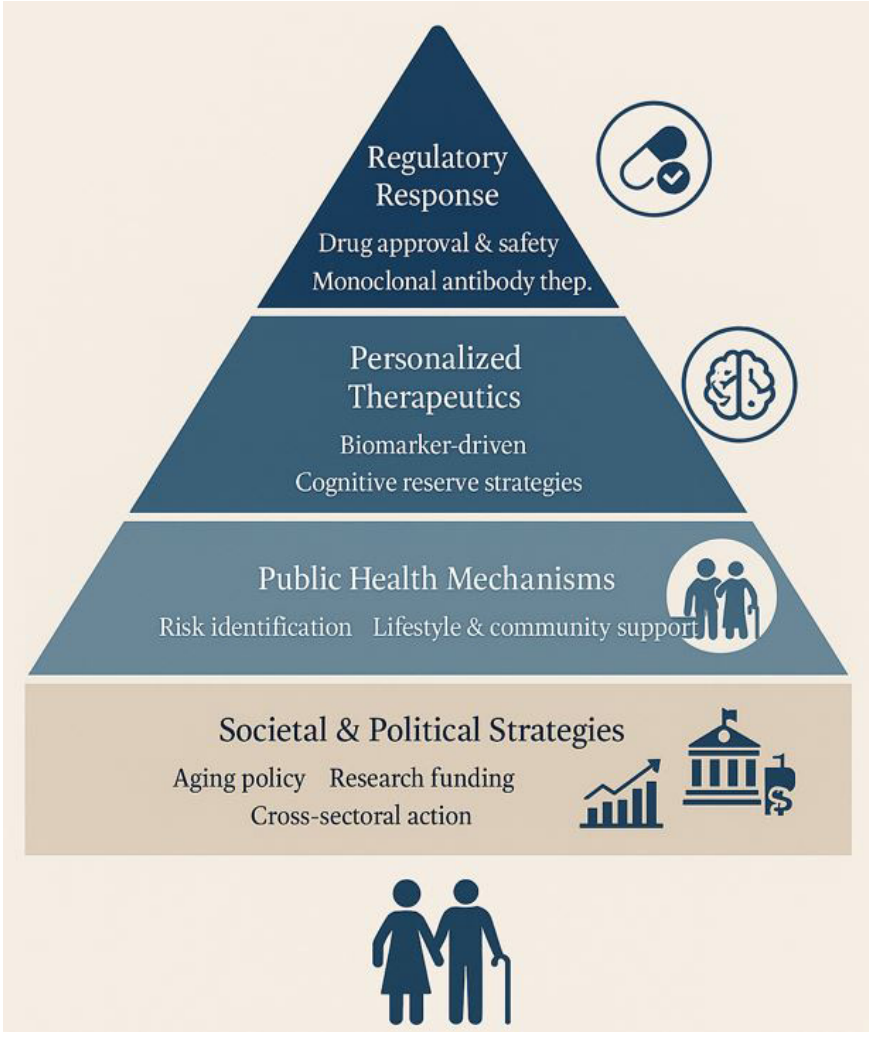

Figure 2. From drug approval to societal strategy: A multilevel framework for Alzheimer's disease
Note. Created by the author.

On the other hand, modifying the 14 risk factors identified by the Lancet Commission could potentially prevent or delay up to half of all dementia cases. However, achieving this goal requires more than individual-level interventions; it necessitates national and international government policy changes, prioritizing high-risk populations, and implementing personalized intervention strategies (Livingston et al., 2024). One of the important potentials for our country is the

creation of a database such as e-NABIZ. It seems possible to collect data from this data that will show real risks, as Yiğit et al. (2024) did. The same system can be used for screenings and risk warnings that will consist of several phases.

Targets such as improving dementia care and implementing holistic state plans aimed at early diagnosis and risk reduction, like Japan's Orange Plan, which anticipates that approximately 10% of the population will face cognitive decline in the next few decades, can be planned (Japan Health Policy NOW – The New Orange Plan, 2015). In addition, many policies and actions can be rapidly developed, such as creating an institute dedicated to this field within the Presidency of the Turkish Health Sciences Institutes (TUSEB), which was established for strategy development and, if necessary, project financing.

CONCLUSION

In conclusion, regulatory authorities can no longer approach the issue solely through the narrow lens of approving or rejecting newly developed disease-modifying treatments for Alzheimer's disease (AD). We are facing an aging population, a rise in neurodegenerative disorders, and a growing burden of Alzheimer's-related dementias—factors that demand new and diverse approaches and political strategies at the societal level.

Such policy planning must be multi-dimensional. While developing personalized therapeutic strategies is essential, the broader public health and societal dimensions must not be overlooked. Health authorities must begin to adopt a comprehensive view of aging and dementia in our country to address the emerging societal burden of dementia in the coming years. This includes supporting research that considers all relevant aspects of the disease, promoting public health through multiple mechanisms, identifying individuals at risk, and delivering personalized management strategies through practical and proactive government policies.

Ethical Approval: This study does not involve human participants, clinical interventions, or data requiring ethical committee approval. Therefore, ethical approval was not necessary.

Authors' Contributions: LH conceptualized the study design. DE conducted the literature review and wrote the draft. BT participated in draft

writing and formatting. LH and TA contributed to the review and editing processes. All the authors participated in the results and discussion. All authors read and approved the final version of the manuscript.

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