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Global Burden of Alzheimer's Disease Attributable to High Fasting Plasma Glucose: Epidemiological Trends and Machine Learning Insights

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Purpose: High fasting plasma glucose (HFPG) is a known risk factor for Alzheimer's disease (AD). This study aims to analyze global trends in AD death rates and disability-adjusted life years (DALYs) rates attributable to HFPG from 1990 to 2021 and assess the potential of glucose-related biomarkers in predicting cognitive impairment.

Methods: Data from the Global Burden of Disease 2021 database were used to analyze AD death rates and DALY rates due to HFPG across 204 countries. All rates were age-standardized. Joinpoint regression, age-period-cohort models, and ARIMA were employed to analyze trends and make future predictions. NHANES data were used to build machine learning models (including logistic regression, SVM, random forests, etc). to evaluate glucose-related biomarkers in predicting cognitive impairment.

Results: From 1990 to 2019, global AD death rates attributable to HFPG increased from 2.64 (95% UI: 0.11, 8.38) to 3.73 (95% UI: 0.15, 11.84), with the highest increases in high-income North America, North Africa, and Sub-Saharan Africa. DALY rates also rose globally, from 47.07 (95% UI: 2.72, 126.46) to 66.42 (95% UI: 3.83, 178.85). The greatest impact was observed in females, particularly those aged 80 and above. Joinpoint analysis indicated a significant rise in death rates from 1995 to 2000, followed by a slower increase in recent years. ARIMA model predictions indicate a gradual decline in death rates and DALY rates over the next 15 years. Logistic regression models showed the highest accuracy (90.4%) in predicting cognitive impairment, with 2-hour postprandial glucose and fasting plasma glucose being key predictors.

Conclusion: From 1990 to 2021, global AD death rates and DALY rates due to HFPG significantly increased, with a greater burden in females and regions with higher socio-demographic development. Machine learning models are effective tools for identifying individuals at high risk of elevated blood glucose leading to cognitive impairment.

Keywords: epidemiology, diabetes, cognitive decline, disability-adjusted life years, machine learning, public health

Introduction

AD is a prevalent neurodegenerative disorder characterized by progressive memory loss, cognitive decline, and behavioral changes. With the rapid aging of the global population, the prevalence of AD has increased significantly. According to the World Alzheimer Report 2023, approximately 55 million people are currently living with AD worldwide, and this number is projected to rise to 139 million by 2050.[1] Moreover, the economic burden of dementia is expected to more than double by 2030, from $1.3 trillion annually in 2019 to $2.8 trillion.[2]

In light of these figures, the adage "prevention is better than cure" has become particularly pertinent. The 2020 Lancet Commission on dementia prevention, intervention, and care identified 12 modifiable risk factors that could prevent or

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delay up to 40% of dementia cases.[3] Among these, HFPG was found to have a sufficiently strong causal link to Alzheimer's disease and other dementias. Fasting plasma glucose (FPG) is an important clinical indicator for diagnosing and monitoring diabetes and prediabetes, and its levels have been rising globally, with particularly rapid increases in low- and middle-income countries.[4,5]

Emerging evidence highlights the molecular interplay between hyperglycemia and AD pathogenesis. Elevated FPG induces insulin resistance within neurons, disrupting glucose metabolism, which is essential for normal neuronal function.[6] This metabolic dysregulation promotes the overproduction and aggregation of amyloid-beta (Aβ), a neurotoxic peptide that forms plaques and disrupts synaptic function, both hallmark features of AD, through dysregulated insulin-degrading enzyme activity.[7] Additionally, hyperglycemia accelerates Tau protein hyperphosphorylation via activation of glycogen synthase kinase-3β (GSK-3β).[8] The hyperglycemia increases oxidative stress and neuroinflammation, which damage the blood-brain barrier (BBB), facilitating the entry of harmful substances into the brain and exacerbating AD pathology.[9] Chronic hyperglycemia is also linked to altered brain metabolism, neuronal loss, and increased excitability, which in turn promote Aβ aggregation and accelerate AD progression.[10]

Machine learning (ML) and data science are increasingly valued in epidemiology and cognitive function research for analyzing complex, high-dimensional data, enhancing predictions of cognitive impairment progression, particularly the transition from mild cognitive impairment (MCI) to AD. Ansart et al[11] demonstrated that combining cognitive assessments with brain imaging variables like FDG-PET enhances MCI-to-AD progression prediction, while Kang et al[12] showed that deep learning models trained on multi-center neuropsychological data achieve high predictive accuracy. Ezzati et al[13] highlighted the importance of features like hippocampal volume and demographic data, showing that ML models can accurately classify cognitively normal (CN) individuals from AD patients. Furthermore, Grassi et al[14] developed a model using demographic and neuropsychological data to identify individuals at high risk of MCI-to-AD conversion. However, these approaches are time-intensive and inconsistent, limiting their use in primary care; thus, we aim to develop an accessible cognitive impairment risk assessment model based on readily available indicators, such as glucose-related physiological markers.

Building on these findings, we aimed to quantify the global burden of AD attributable to HFPG and to identify trends from 1990 to 2021 using data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD).[15]

Focusing on death rates and DALY rates, all age-standardized, we examined the relationship between sociodemographic indicators and HFPG-related AD burden. Complementing this analysis, we applied multiple machine learning models, such as logistic regression, support vector machines (SVM), and random forests, alongside others, all trained on Nutrition Examination Survey (NHANES) data. Using glucose-related biomarkers such as FPG, 2-hour postprandial glucose, and glycated hemoglobin (HbA1c), our approach helped identify the most predictive model, ultimately improving our ability to detect individuals at heightened risk for developing AD.

Materials and Methods

Study Data

We used data from the GBD 2021 study, which assesses health loss across 204 countries and territories using standardized methodologies. The study focused on AD attributable to HFPG. All data presented in this paper, including death rates and DALY rates, are age-standardized rates. These rates were assessed at the global, regional, and national levels, with 95% uncertainty intervals (UI) included.

Additionally, we utilized NHANES data (2011–2014), which included cognitive function tests, diabetes-related surveys, and laboratory tests such as fasting glucose and the oral glucose tolerance test. Cognitive impairment was identified using established cut-offs for the Animal Fluency Test (AFT) (<14) and Digit Symbol Substitution Test (DSST) (<34).[16,17] Participants with incomplete data, inconsistent answers, or those who declined to respond were excluded from the analysis.

Analytical Approaches

Age-Period-Cohort Model

The Age-Period-Cohort (APC) model was used to analyze how age, period, and cohort factors influence AD death rates attributable to HFPG. A log-linear regression model was applied to assess the effects of age, period, and cohort on AD-

related death, incorporating coefficients for each factor along with an intercept and residuals. The intrinsic estimator (IE) method was used to evaluate the net effects of these dimensions on the trends observed.

Joinpoint Analysis

Joinpoint Software (Command Line Version 4.5.0.1) from the US National Cancer Institute was used to assess trends in AD attributable to HFPG. A segmented line model on a logarithmic scale was applied to calculate average annual percentage changes (AAPCs) with 95% confidence intervals (CIs). AAPCs above zero indicate an upward trend in AD rates, while stability is inferred if the 95% CI includes zero. This analysis aimed to determine whether HFPG has influenced AD trends from 1990 to 2021.

Frontier Analysis

This method evaluated the AD burden attributable to HFPG in relation to sociodemographic development across different SDI regions. A non-linear frontier was created to represent the achievable burden based on development status. Non-parametric data envelope analysis quantified the gap between the observed DALY rate and the frontier, highlighting potential health gains by reducing the burden in high-burden regions to the levels seen in low-burden regions.

Autoregressive Integrated Moving Average (ARIMA) Model

The ARIMA model was used to predict future trends in death rates and DALY rates due to HFPG. ARIMA assumes that the time series data are dependent on past values and random shocks, incorporating autoregressive (AR) and moving average (MA) components, as well as differencing to ensure stationarity. The model was applied to the time series of death rates and DALY rates attributable to HFPG, allowing for the prediction of future trends based on historical data.

Machine Learning Analysis

The machine learning analysis evaluated the predictive value of glucose-related indicators for cognitive impairment using various machine learning models through analyses conducted in Python 3.13.0. After removing missing values, a cleaned dataset of 942 NHANES data points was used, with diabetes questionnaire responses, glycohemoglobin, fasting glucose, and 2-hour postprandial glucose as predictor variables and cognitive impairment status as the target variable. The dataset was split into training and testing sets in an 8:2 ratio and standardized for consistency. Models constructed included logistic regression, support vector machines (SVM), random forests, K-nearest neighbors, decision tree, and gradient boosting, as well as an ensemble voting classifier that combined predictions from the base models using hard voting. Each model was trained on the training set and evaluated on the test set, with 10-fold cross-validation used to assess model stability. Performance was measured using metrics such as accuracy, recall, specificity, negative predictive value (NPV), false positive rate (FPR), false negative rate (FNR), false discovery rate (FDR), F1 score, Brier score, area under the curve (AUC), and average precision score (APS). Results were consolidated to allow for a comprehensive comparison of each model's effectiveness in predicting cognitive impairment. The machine learning process is shown in Figure 1.

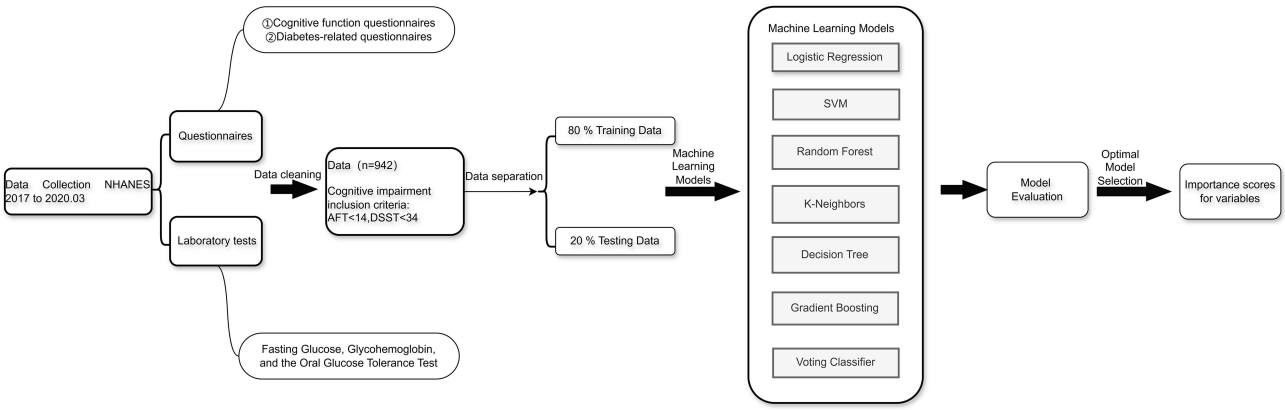

Figure 1 Machine Learning Flowchart.

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Statistical Analysis

Following the methodologies outlined in previous GBD Study 2021 research, we computed a 95% UI for each variable, standardizing rates per 100,000 population. Two-sided tests were performed, with P values < 0.05 considered significant. All statistical analyses and graphical representations were conducted using R version 4.3.2.

Results

Overview of the Global Burden

In our analysis of the global death rates of AD attributable to HFPG, we observed an increase from 2.64 (95% UI: 0.11, 8.38) in 1990 to 3.73 (95% UI: 0.15, 11.84) in 2019. This increase was particularly pronounced in High-income North America (5.66, 95% UI: 0.23, 18.07), North Africa and the Middle East (4.89, 95% UI: 0.19, 15.67), Central Sub-Saharan Africa (4.7, 95% UI: 0.18, 15.26), Tropical Latin America (4.04, 95% UI: 0.17, 12.44), and Oceania (4.01, 95% UI: 0.15, 13.44). (Table 1, Figure 2A).

The DALY rates of AD attributable to HFPG also increased more rapidly worldwide, from 47.07 (95% UI: 2.72, 126.46) in 1990 to 66.42 (95% UI: 3.83, 178.85) in 2019. Significant increases were observed in High-income North America (99.65, 95% UI: 5.91, 264.59), North Africa and the Middle East (91.57, 95% UI: 5.33, 245.55), Central Sub-Saharan Africa (80.9, 95% UI: 4.25, 226.58), Tropical Latin America (76.27, 95% UI: 4.36, 204.86), and Oceania (75.67, 95% UI: 4.18, 205.9). (Table 1, Figure 2B).

Table 1 Global Burden of the Death and DALYs Rate of AD Attributable to HFPG in 2021

Death		1990		2021	
Characteristics	**Sex**	**Deaths Number [95% UI]**	**Age-Standardized Rate (95% UI)**	**Deaths Number [95% UI]**	**Age-Standardized Rate (95% UI)**
Global	Male	23067 (904,74,594)	2.3 (0.09,7.47)	98,900 (3914,316,131)	3.26 (0.13,10.51)
Global	Female	48403 (1950,148,604)	2.83 (0.11,8.93)	191,132 (7845,600,477)	4.03 (0.17,12.61)
Global	Both	71471 (2849,221,701)	2.64 (0.11,8.38)	290,032 (11,760,916,714)	3.73 (0.15,11.84)
Low SDI	Male	882 (31,2904)	1.77 (0.06,5.89)	3109 (111,10,140)	2.47 (0.09,8.2)
Low SDI	Female	1143 (43,3721)	2.05 (0.08,6.53)	4648 (169,14,934)	3.12 (0.11,10.25)
Low SDI	Both	2025 (74,6573)	1.91 (0.07,6.19)	7757 (280,25,001)	2.83 (0.1,9.31)
Low-middle SDI	Male	2745 (101,8906)	1.69 (0.06,5.51)	11,674 (433,38,369)	2.76 (0.1,9.17)
Low-middle SDI	Female	3649 (134,11,687)	2.13 (0.08,6.71)	18,927 (701,60,639)	3.52 (0.13,11.44)
Low-middle SDI	Both	6394 (235,20,481)	1.92 (0.07,6.09)	30,601 (1134,98,703)	3.19 (0.12,10.43)
Middle SDI	Male	5345 (201,17,754)	2.25 (0.08,7.34)	24,375 (947,78,104)	2.91 (0.11,9.26)
Middle SDI	Female	9524 (365,30,333)	2.94 (0.11,9.36)	44,959 (1759,143,574)	3.77 (0.15,12.14)
Middle SDI	Both	14869 (563,48,060)	2.66 (0.1,8.58)	69,335 (2707,219,022)	3.42 (0.13,10.92)
High-middle SDI	Male	5182 (203,17,193)	2.29 (0.09,7.43)	20,918 (845,67,946)	3.09 (0.12,9.93)
High-middle SDI	Female	12374 (494,38,772)	2.76 (0.11,8.76)	45,041 (1835,139,994)	3.79 (0.15,11.75)
High-middle SDI	Both	17556 (697,55,920)	2.61 (0.1,8.38)	65,959 (2681,205,257)	3.54 (0.14,11.11)
High SDI	Male	8886 (368,28,342)	2.64 (0.11,8.64)	38,734 (1577,124,186)	3.87 (0.16,12.41)
High SDI	Female	21659 (913,67,725)	3 (0.13,9.43)	77,380 (3262,239,140)	4.51 (0.19,13.97)
High SDI	Both	30545 (1283,95,703)	2.88 (0.12,9.17)	116,115 (4821,364,124)	4.27 (0.18,13.27)
Andean Latin America	Both	193 (7,635)	1.21 (0.05,3.99)	1124 (45,3660)	2.07 (0.08,6.73)

(*Continued*)

Table 1 (Continued).

Australasia	Both	470 (20,1493)	2.26 (0.1,7.24)	1954 (84,5953)	3 (0.13,9.17)
Caribbean	Both	477 (18,1576)	2.34 (0.09,7.89)	1576 (62,5158)	2.77 (0.11,9.07)
Central Asia	Both	491 (19,1627)	1.39 (0.05,4.67)	1477 (51,4918)	2.67 (0.09,9.01)
Central Europe	Both	2626 (104,8450)	2.39 (0.09,7.83)	8628 (348,27,518)	3.52 (0.14,11.21)
Central Latin America	Both	1413 (54,4588)	2.4 (0.09,7.84)	6645 (261,21,540)	2.91 (0.11,9.44)
Central Sub-Saharan Africa	Both	286 (12,888)	3.53 (0.15,11.07)	1125 (43,3565)	4.7 (0.18,15.26)
East Asia	Both	13420 (534,44,750)	3.31 (0.13,10.45)	61,212 (2426,189,557)	3.62 (0.14,11.46)
Eastern Europe	Both	2969 (112,9582)	1.46 (0.05,4.81)	8181 (308,26,023)	2.27 (0.08,7.25)
Eastern Sub-Saharan Africa	Both	659 (24,2194)	2.02 (0.07,6.75)	2282 (78,7466)	2.57 (0.09,8.6)
High-income Asia Pacific	Both	5807 (260,17,465)	3.78 (0.17,11.46)	29,848 (1409,88,269)	4 (0.19,11.88)
High-income North America	Both	11460 (500,35,028)	3.09 (0.14,9.47)	43,128 (1762,137,445)	5.66 (0.23,18.07)
North Africa and Middle East	Both	3068 (119,9854)	3.2 (0.13,10.32)	14,262 (574,45,460)	4.89 (0.19,15.67)
Oceania	Both	41 (2,135)	3.6 (0.14,12.1)	140 (5,463)	4.01 (0.15,13.44)
South Asia	Both	5029 (176,16,405)	1.71 (0.06,5.56)	27,989 (1029,90,776)	2.87 (0.1,9.42)
Southeast Asia	Both	3448 (126,11,276)	2.4 (0.09,7.87)	15,380 (568,51,424)	3.58 (0.13,11.99)
Southern Latin America	Both	734 (28,2415)	1.99 (0.08,6.51)	2949 (116,9427)	3.15 (0.12,10.08)
Southern Sub-Saharan Africa	Both	475 (16,1570)	2.64 (0.09,8.79)	1270 (45,4344)	3.56 (0.12,12.35)
Tropical Latin America	Both	1955 (77,6265)	3.31 (0.13,10.48)	9628 (403,29,679)	4.04 (0.17,12.44)
Western Europe	Both	15706 (624,49,392)	2.69 (0.11,8.61)	48,690 (1947,153,966)	3.71 (0.15,11.65)
Western Sub-Saharan Africa	Both	742 (28,2437)	1.55 (0.06,5.12)	2545 (88,8559)	2.36 (0.08,8.03)
DALYs		**1990**		**2021**	
Characteristics	**Sex**	**DALYs number [95% UI]**	**Age-standardized rate (95% UI)**	**DALYs number [95% UI]**	**Age-standardized rate (95% UI)**
Global	Male	497842 (28,468,1,368,862)	40.93 (2.36,112.07)	1,929,129 (109,742,5,194,918)	57.71 (3.29,155.61)
Global	Female	943698 (54,235,2,541,833)	50.81 (2.93,136.84)	3,419,725 (198,318,9,146,429)	72.55 (4.21,193.7)
Global	Both	1441540 (82,703,3,878,462)	47.07 (2.72,126.46)	5,348,854 (308,060,14,351,156)	66.42 (3.83,178.85)
Low SDI	Male	20113 (1108,55,191)	31.37 (1.72,87.68)	66,461 (3377,186,816)	43.27 (2.2,124)
Low SDI	Female	25570 (1364,70,055)	37.29 (1.99,101.63)	95,626 (4860,269,310)	54.86 (2.79,153.91)
Low SDI	Both	45683 (2472,125,243)	34.41 (1.86,93.92)	162,087 (8237,452,611)	49.47 (2.52,139.57)
Low-middle SDI	Male	62157 (3529,166,519)	31.62 (1.78,85.73)	245,474 (13,242,699,707)	49.93 (2.69,142.12)
Low-middle SDI	Female	80505 (4357,215,733)	39.95 (2.17,106.25)	376,652 (20,232,1,017,030)	63.39 (3.41,173.52)
Low-middle SDI	Both	142662 (7887,378,740)	35.92 (1.99,95.66)	622,127 (33,437,1,710,189)	57.36 (3.09,158.52)
Middle SDI	Male	123053 (6716,341,318)	40.93 (2.25,114.66)	517,510 (28,852,1,401,854)	53.36 (2.96,143.44)
Middle SDI	Female	204872 (11,096,562,046)	54 (2.92,149.19)	893,599 (51,310,2,418,273)	70.76 (4.06,191.57)
Middle SDI	Both	327924 (17,812,901,711)	48.47 (2.64,133.72)	1,411,109 (80,072,3,799,735)	63.35 (3.6,172.97)
High-middle SDI	Male	113145 (6469,315,164)	40.27 (2.32,109.65)	417,548 (24,021,1,111,697)	55.55 (3.18,147.43)
High-middle SDI	Female	244672 (14,110,668,081)	49.14 (2.83,134.02)	820,046 (49,112,2,165,511)	69.86 (4.18,183.97)

(*Continued*)

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Table 1 (Continued).

High-middle SDI	Both	357816 (20,579,978,893)	46.12 (2.66,124.91)	1,237,594 (73,043,3,272,973)	64.33 (3.8,170.88)
High SDI	Male	178778 (10,649,477,451)	46.63 (2.79,124.98)	680,390 (40,369,1,802,555)	67.74 (4.02,180)
High SDI	Female	386971 (23,166,1,016,464)	53.6 (3.21,140.55)	1,230,586 (72,614,3,285,985)	80.12 (4.74,211.61)
High SDI	Both	565750 (33,896,1,492,491)	51.18 (3.07,135.29)	1,910,976 (112,984,5,105,647)	75.11 (4.45,198.51)
Andean Latin America	Both	3924 (220,10,501)	23.22 (1.3,61.77)	21,937 (1253,59,873)	39.74 (2.27,108.36)
Australasia	Both	9184 (593,24,346)	41.29 (2.61,109.78)	33,122 (2069,86,659)	53.45 (3.37,140.67)
Caribbean	Both	10332 (591,28,014)	45.81 (2.58,124.65)	30,087 (1731,79,956)	54.44 (3.15,143.84)
Central Asia	Both	10000 (556,27,027)	26.09 (1.43,71.86)	30,980 (1628,90,205)	50.89 (2.64,148.85)
Central Europe	Both	56073 (3411,149,742)	44.82 (2.72,120.49)	160,790 (9663,419,379)	65.91 (3.96,171.31)
Central Latin America	Both	32488 (1960,85,550)	49.62 (2.94,130.32)	137,130 (8083,365,354)	59.09 (3.48,158.37)
Central Sub-Saharan Africa	Both	6810 (389,17,810)	61.21 (3.49,163.56)	24,293 (1295,67,877)	80.9 (4.25,226.58)
East Asia	Both	294748 (16,203,827,599)	56.22 (3.1,154.24)	1,246,621 (73,202,3,299,331)	66.37 (3.89,176.69)
Eastern Europe	Both	63685 (3629,177,123)	27.35 (1.55,75.53)	156,198 (8873,425,390)	42.84 (2.44,117.18)
Eastern Sub-Saharan Africa	Both	13916 (704,39,354)	34.28 (1.72,96.43)	45,666 (2148,132,676)	43.8 (2.07,126.35)
High-income Asia Pacific	Both	106880 (6747,271,520)	63.12 (3.95,161.32)	451,644 (28,330,1,154,338)	68.17 (4.29,174.66)
High-income North America	Both	213369 (13,109,557,946)	57.2 (3.52,148.96)	731,687 (43,232,1,958,234)	99.65 (5.91,264.59)
North Africa and Middle East	Both	66256 (3761,180,361)	59.36 (3.36,161.27)	300,182 (17,506,793,108)	91.57 (5.33,245.55)
Oceania	Both	1032 (60,2917)	67.24 (3.8,189.18)	3296 (189,8939)	75.67 (4.18,205.9)
South Asia	Both	115263 (6295,304,137)	32.12 (1.76,87.08)	569,302 (30,292,1,590,852)	51.08 (2.72,142.69)
Southeast Asia	Both	74194 (4016,202,006)	44.42 (2.34,122.98)	309,894 (16,184,870,214)	64.21 (3.31,182.73)
Southern Latin America	Both	15032 (910,40,436)	37.22 (2.24,100.3)	53,986 (3168,142,991)	58.3 (3.42,154.79)
Southern Sub-Saharan Africa	Both	9356 (456,26,858)	47.16 (2.29,136.25)	26,566 (1371,76,342)	64.33 (3.31,187.21)
Tropical Latin America	Both	41886 (2312,117,131)	61.55 (3.44,169.07)	185,362 (10,590,498,434)	76.27 (4.36,204.86)
Western Europe	Both	282168 (16,228,751,568)	46.35 (2.67,124.41)	779,500 (43,784,2,116,189)	63.81 (3.6,173.67)
Western Sub-Saharan Africa	Both	14945 (802,41,309)	26.33 (1.4,73.22)	50,610 (2521,144,778)	40.06 (1.99,116.54)

Females older than 50 years were susceptible to the disease burden of AD attributable to HFPGThe global data on deaths and DALYs for AD attributable to HFPG by age group (Figure 3A) show a significant increase, particularly among females, when compared to specific values from 1990 and 2021 (Figure 3B and C). In 2021, the highest number of deaths occurred in the 80–89 age group, with female deaths in this group being twice that of males (Figure 3B). DALYs also peaked in this age range, with females surpassing males starting from age 50. These findings demonstrate a growing disease burden in females compared to males, with a notable rise in both deaths and DALYs from 1990 to 2021. Comparing 1990 to 2021, there was a sharp increase in both deaths and DALYs for AD attributable to HFPG, particularly in females aged 80 and above. This emphasizes the increasing impact of HFPG on older females and highlights the need for targeted healthcare strategies to address this growing issue.

Burden of AD Attributable to HFPG Across SDI Quintiles and Regions

We conducted a further sub-analysis of deaths and DALYs numbers based on SDI regions. Our results indicate that, from 1990 to 2021, the top three SDI regions for AD deaths and DALYs numbers due to HFPG were High-Middle, High, and

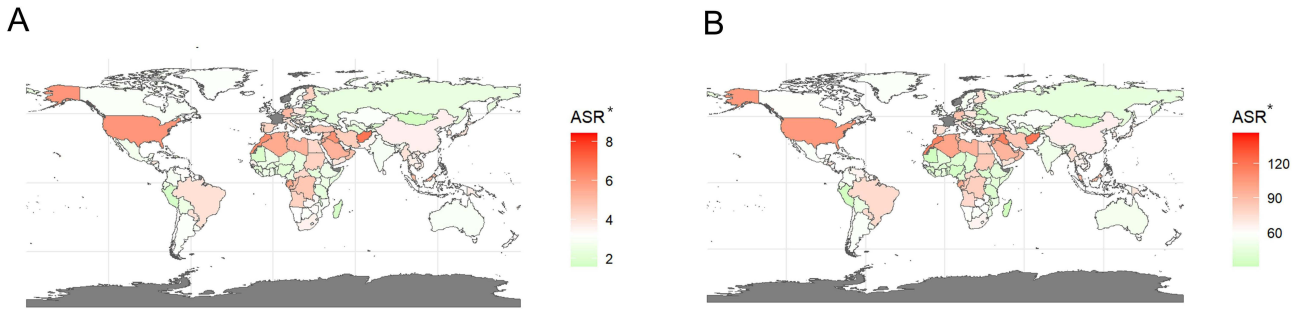

Figure 2 (**A**) Global death rates map in 2021. (**B**) Global DALY rates map in 2021. *ASR: Age-Standardized rate.

Lower-Middle. (Figure 4A). From 1990 to 2021, East Asia, Western Europe, and High-income North America had the largest increases in both AD deaths and DALYs. East Asia, in particular, saw a dramatic rise, with deaths increasing from 294,748 to 1,246,621 and DALYs from 357,816 to 1,237,594 (Figure 4B). Western Europe and High-income North America also experienced substantial increases, with Western Europe's deaths rising from 282,168 to 779,500 and DALYs from 560,730 to 1,609,790.In contrast, low SDI regions like Eastern Sub-Saharan Africa saw more modest increases in deaths (from 13,916 to 45,666) and DALYs (from 68,149 to 206,956), but still reported lower totals compared to high SDI regions. These trends highlight the growing disparity in AD burden across regions, with high SDI regions showing the most significant increases.

Joinpoint Analysis of AD Attributable to HFPG Death Rates Globally

The Joinpoint analysis revealed significant trends in AD death rates attributable to HFPG from 1990 to 2021 (Figure 5). The most notable increases occurred between 1995 and 2000, with an AAPC of 2.3994% (95% CI: 2.2706 to 2.5285) for both sexes combined, 2.4237% (95% CI: 2.2882 to 2.5594) for females, and 2.4356% (95% CI: 2.2969 to 2.5745) for males. In recent years (2015–2021), the rate of increase slowed significantly, with AAPCs of 0.2637% (95% CI: 0.1966 to 0.3308) for both sexes and 0.3336% (95% CI: 0.2627 to 0.4045) for females. Males exhibited a slight decline in AAPC from 2018 to 2021, suggesting a stabilization in the death rates.

The Effects of Age, Period, and Cohort on Global Death Rates

In this global APC analysis of death rates for AD attributable to HFPG from 1992 to 2021, several significant patterns emerged across different age groups (Figure S1).

Age-Specific Death Rates

The analysis revealed that the highest death rates occurred in the 95+ age group, with a rate of 546.21 per 100,000 (95% CI: 540.31 to 552.18). Death rates increased significantly with age, with notable increases particularly in the 85–95+ age range (including the 85–89 and 90–94 age groups). These findings align with the global trend of aging populations, showing a marked rise in HFPG-related AD mortality as individuals reach older age groups.

Period-Specific Death Trends

Period-specific analysis showed a consistent upward trend in death rates from 1992 to 2021. The 1992–1996 period had a death rate of 3.245 per 100,000 (95% CI: 3.2003 to 3.2903), whereas the 2017–2021 period saw a significant rise to 4.4111 per 100,000 (95% CI: 4.2582 to 4.5695). This represents an approximate 36% increase in the death rate over the three decades, signaling a rise in HFPG-related AD mortality globally. The 2002–2006 period (3.8187 per 100,000) to the 2017–2021 period illustrates a dramatic shift in the global burden of AD, with the death rate showing a more rapid increase post-2010.

Cohort-Specific Death Rates

Cohort analysis indicated that individuals born around 1977 exhibited the highest death rate ratio of 1.7341 (95% CI: 0.8476 to 3.5477). This suggests that those born in 1977 experienced higher death rates than other cohorts, potentially influenced by unique environmental, lifestyle, or genetic factors.

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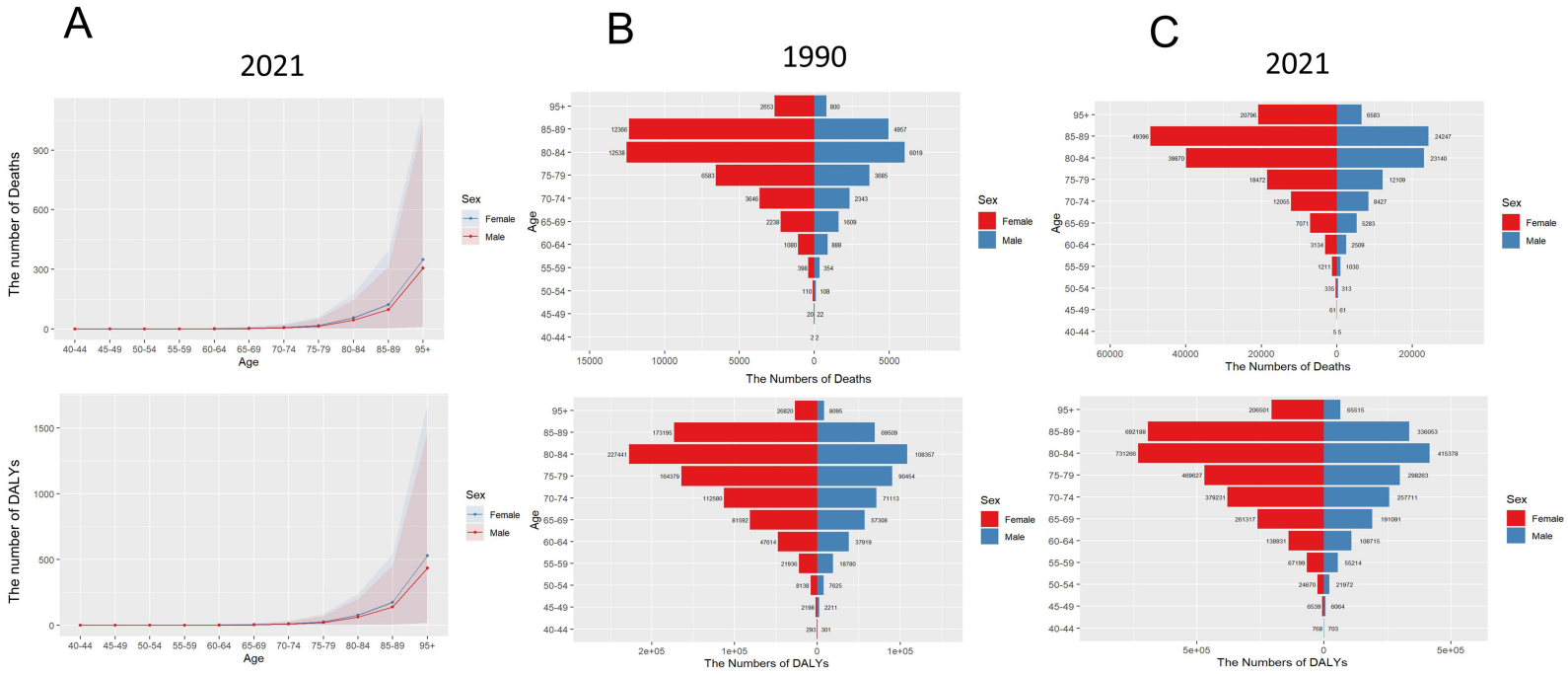

Figure 3 Global Burden of AD Attributable to HFPG by Age and Gender (1990 vs 2021) (**A**) Death rates and DALY rates. (**B**) Age-Specific death and DALYs number in 1990(**C**) Age-Specific death and DALYs number in 2021.

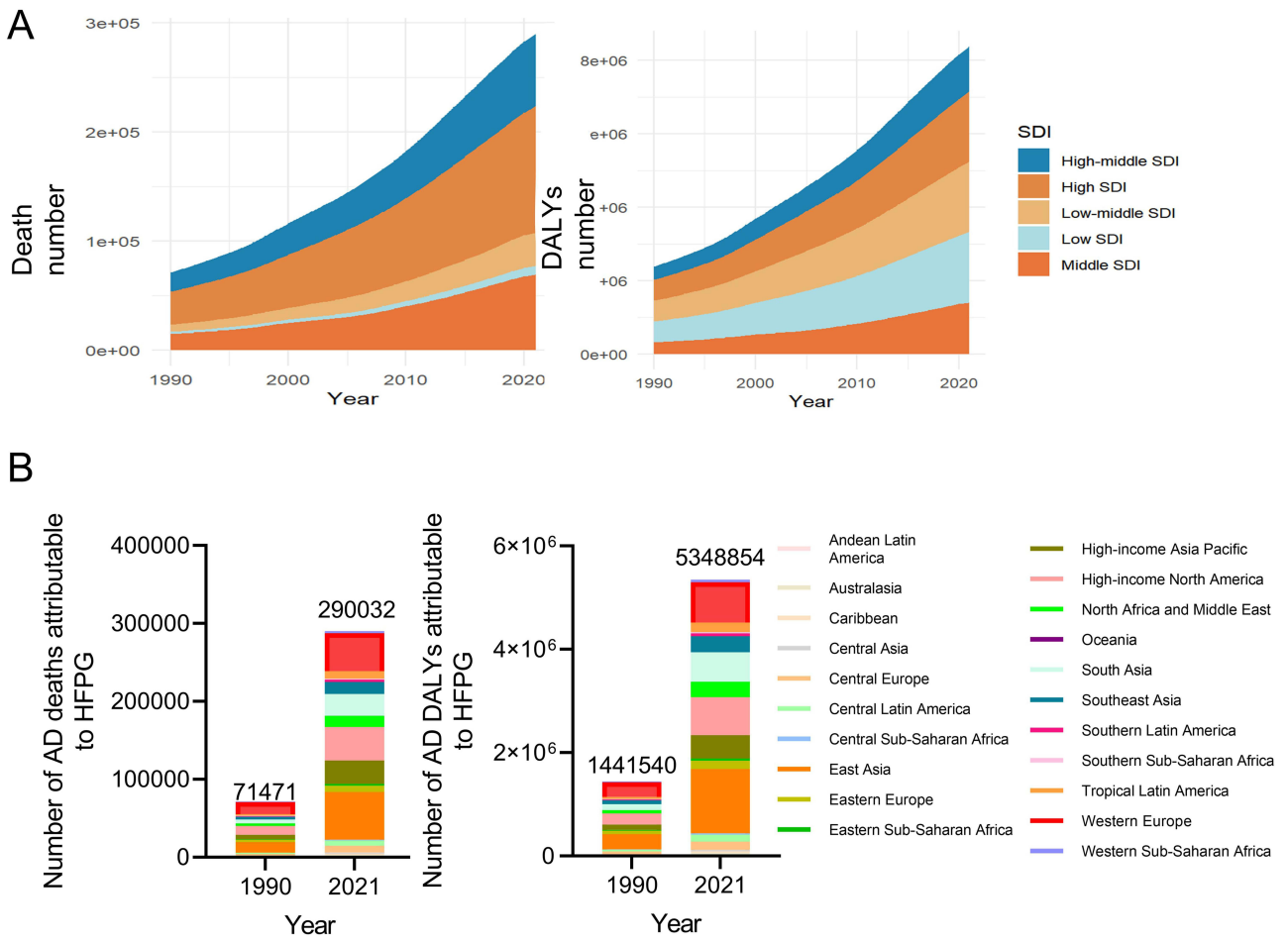

Figure 4 Global and Regional Trends in AD Attributable to HFPG Burden (**A**) Number of death and DALYs due to AD attributable to HFPG globally and across different SDI regions from 1990 to 2021. (**B**) Comparison of AD deaths and DALYs attributable to HFPG in 1990 and 2021, both globally and in different regions.

Combined Age-Period-Cohort Effects

The combined APC analysis revealed significant interactions between age, period, and cohort effects. The most substantial increases in death rates were observed in the 85–95+ age group. Period effects showed a concerning upward trend over the last three decades, while cohort-specific effects indicated that those born around 1977 had significantly higher death rates compared to other cohorts.

Frontier Analysis of DALY Rates

An analysis of DALY rates by SDI categories from 1990 to 2021 reveals significant disparities in health outcomes across different levels of sociodemographic development. Figure 6A and Table S1 illustrate the unrealized health gains among countries or regions at varying development levels. In 2021, the DALYs burden and the effective difference in health improvements across these regions are shown in Figure 6B and Table S1. The data indicate that over the past thirty years, there have been notable differences in the progress and magnitude of changes in DALY rates between higher SDI regions and lower SDI regions. This disparity underscores persistent health inequities and highlights the need for targeted interventions to accelerate health gains.

Prediction of AD Due to HFPG Death and DALYs in the Next Fifteen Years

The ARIMA model was used to forecast trends in attributable death rates and DALY rates due to HFPG over the next 15 years, with a focus on comparing projections by gender. The optimized ARIMA model for death rates (1,2,0) achieved an AIC value of −194.56, while the model for DALY rates (1,2,0) had an AIC of −32.56. These models were both robust,

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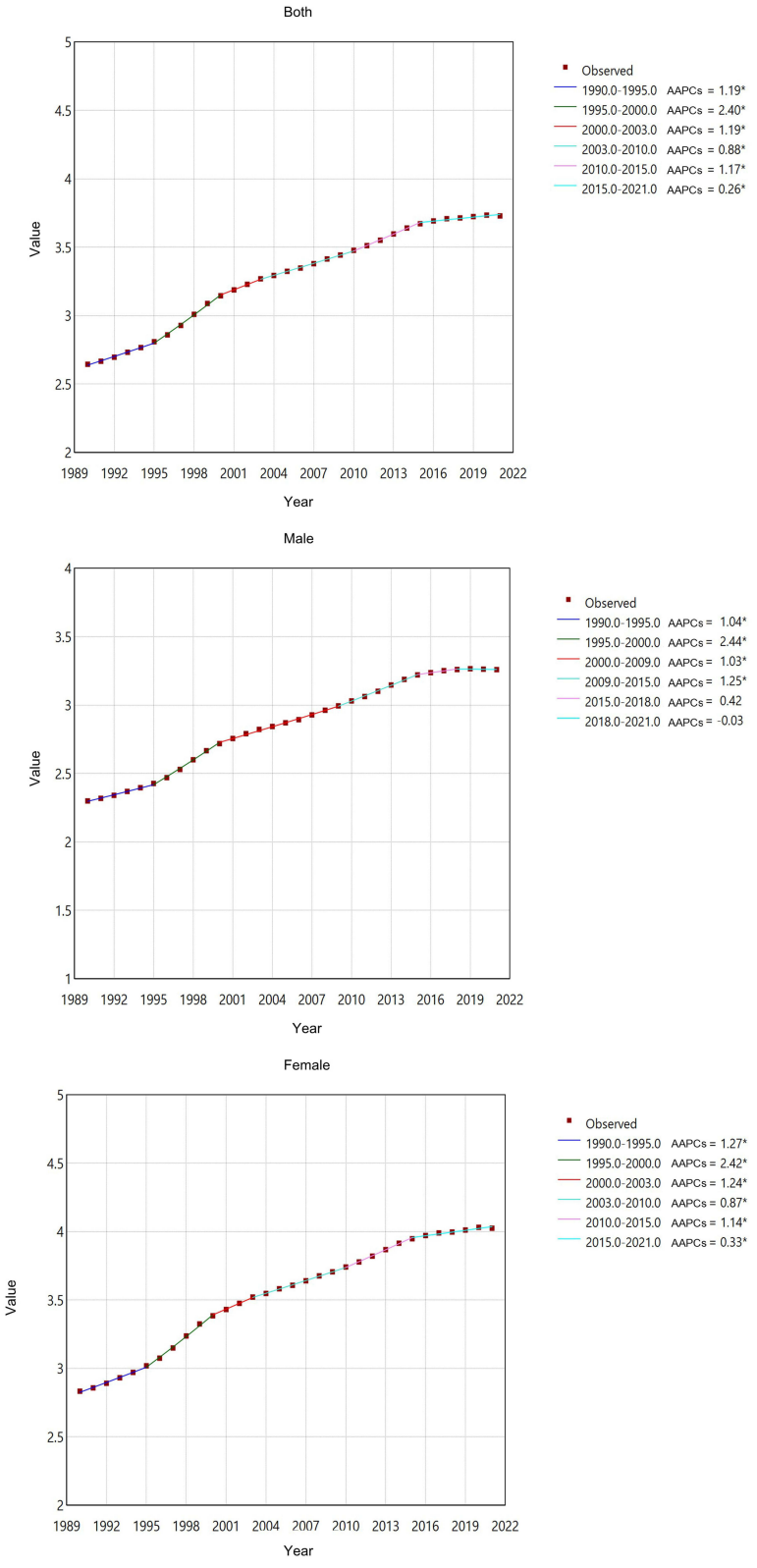

Figure 5 Joinpoint analysis of the sex-specific death rates for AD attributable to HFPG globally from 1990 to 2021. * Indicates that the average annual percentage changes (AAPCs) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: 5 Joinpoints.

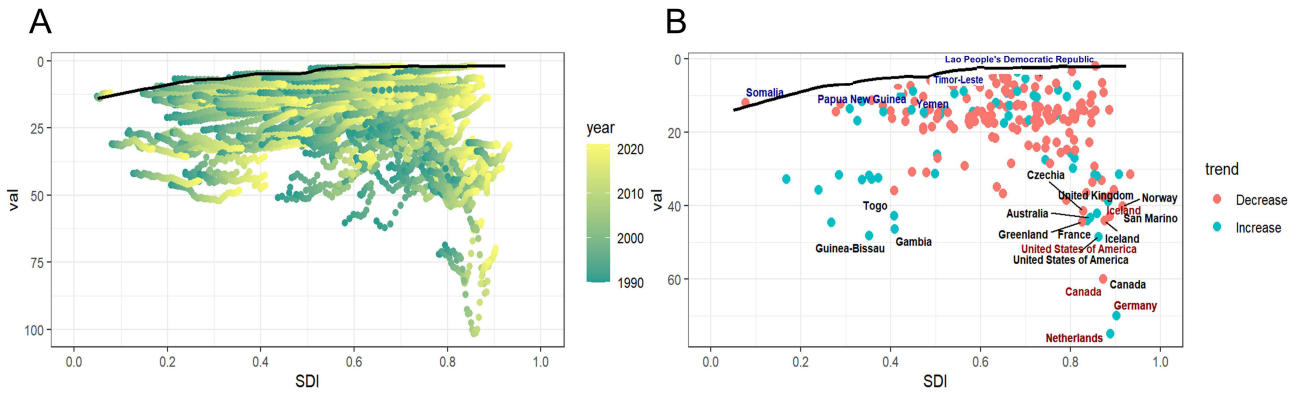

Figure 6 Frontier Analysis Based on SDI from 1990 to 2021, Attributable to AD from HFPG Globally. (**A**) Trend from 1990 to 2021. (**B**) Specific trends of increase or decrease. The frontier is delineated in solid black; countries and territories are represented as dots. The top 15 countries with the largest effective difference (largest early-onset AD DALYs gap from the frontier) are labeled in black. Examples of frontier countries with low SDI (< 0.5) and low effective difference are labeled in blue (eg, Somalia, Lao People's Democratic Republic, Timor-Leste, Papua New Guinea, and Yemen). Examples of countries and territories with high SDI (> 0.85) and relatively high effective difference frontier level of development are labeled in red (eg, Canada, Germany, Netherlands, United States, Iceland). Red dots indicate an increase in AD attributable to HFPG DALY rates from 1990 to 2021; blue dots indicate a decrease in AD attributable to HFPG DALY rates between 1990 and 2021.

with diagnostic tests such as Quantile-Quantile (Q-Q) plots, Autocorrelation Function (ACF)plots, and the Ljung-Box test ($\chi^2 = 3.1604$, P = 0.9774 for death rates, $\chi^2 = 3.7348$, P = 0.9585 for DALY rates) confirming that the residuals were white noise and normally distributed, ensuring the reliability of the forecasts (Figure S2).

The analysis revealed that attributable death rates due to HFPG are expected to decline from 3.7287% in 2021 to 3.5264% in 2036. Similarly, DALY rates are projected to decrease from 66.4249 per 100,000 in 2021 to 64.9446 per 100,000 in 2036, demonstrating a positive trend in reducing the burden of HFPG-related mortality and disability. To provide a more comprehensive understanding of the long-term trends, we examined the death and DALY rate projections by gender. The results indicate that death rates for females are forecasted to decline from 4.0188% in 2022 to 3.9301% in 2036, while male death rates are projected to decrease from 3.2561% in 2022 to 3.2129% in 2036. Similarly, DALY rates for females are expected to decrease from 72.4730 per 100,000 in 2022 to 71.4125 per 100,000 in 2036, whereas male DALY rates are projected to decline from 57.7988 per 100,000 in 2022 to 59.2548 per 100,000 in 2036. (Figure 7A–C, Table S2). Overall, the findings demonstrate a consistent decline in HFPG-related mortality and disability, with gender-specific differences that could inform future public health interventions.

Machine Learning–Based Prediction of Cognitive Impairment Using Glucose-Related Biomarkers

To further investigate the association between hyperglycemia and the risk of cognitive impairment, we utilized cognitive function assessment questionnaires and diabetes-related questionnaires from the NHANES database. Our analysis incorporated key laboratory measurements—HbA1c, 2-hour postprandial glucose, and fasting glucose levels—to train seven machine learning models aimed at predicting the probability of cognitive impairment diagnosis linked to glucose-related biomarkers.

We compared the performance of these models using multiple evaluation metrics. The results indicated that the Logistic Regression and SVM models both exhibited the highest sensitivities (0.904) in predicting cognitive impairment, followed by K-Neighbors (0.899). However, the Support Vector Classifier (SVC) achieved the highest AUC (0.873), demonstrating superior overall discriminative power among the tested models. While the Random Forest and Gradient Boosting models had strong performance in terms of accuracy, they showed relatively lower AUC values (0.5919 and 0.4633, respectively), suggesting that these models were less effective in distinguishing between cognitive impairment and non-impairment cases.

The importance scores from the Logistic Regression model highlighted that 2-hour postprandial glucose was the most influential variable for predicting cognitive impairment, with the highest gain (0.48074). It was followed by fasting glucose levels (0.342735) and HbA1c (0.162635). Interestingly, diabetes-related questionnaires showed minimal predictive value,

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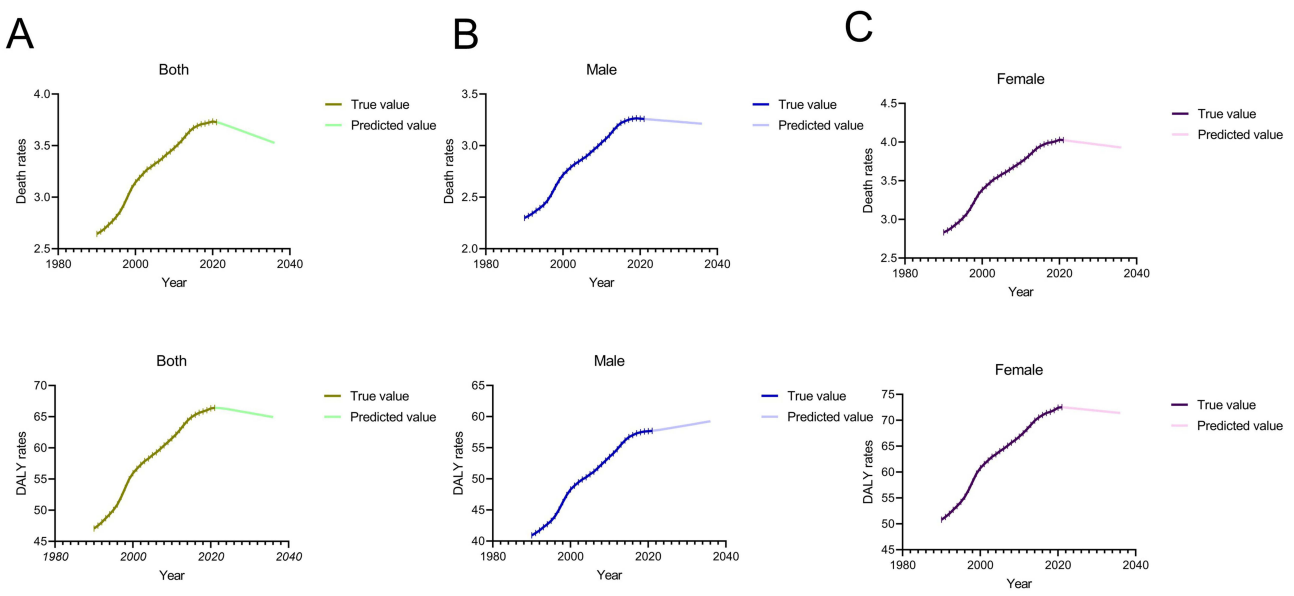

Figure 7 Predicted trends of AD attributable to HFPG death rates and DALY rates globally over the next 15 years (2021–2036). (**A**) Predicted trends for the entire population. (**B**) Predicted trends for males. (**C**) Predicted trends for females. Dark lines represent the true trend of death rates and DALY rates during 1990 to 2021; light lines represent the predicted trend.

with a gain of only 0.013891. This suggests that, although the questionnaires offer some insight into the risk of cognitive decline, they are less reliable than glucose-related biomarkers in predicting cognitive impairment (Table S3). These findings emphasize the relevance of glucose-related biomarkers —particularly postprandial glucose levels—in the identification of individuals at higher risk of cognitive decline.

Discussion

In this study, we provide a comprehensive analysis of the global burden of AD attributable to HFPG from 1990 to 2021. Our findings reveal a significant increase in AD-related deaths and DALYs globally, with the highest burden observed in high SDI regions such as East Asia, Western Europe, and North America. This increase reflects the compounded effects of blood glucose management challenges and aging populations in these regions. This study makes key contributions to the field: First, it presents the first global quantification of sex- and age-specific AD burden attributable to HFPG across 204 countries, revealing important shifts in AD epidemiology. Second, by integrating machine learning with traditional epidemiological methods, we demonstrate the critical predictive value of postprandial glucose—a biomarker often overlooked in AD risk screening.

Recent studies have shown a close relationship between high blood glucose, diabetes, and AD, the latter being characterized by cognitive impairment, memory loss, and pathological features such as Aβ deposition and neurofibrillary tangles (tau protein abnormalities). Epidemiological data suggest that individuals with diabetes have a 1.3 to 5.5 times higher risk of developing AD compared to healthy individuals. Even non-diabetics face increased AD risk with higher glucose levels.[18] Several mechanisms may explain how blood glucose contributes to AD pathogenesis. High blood glucose-induced oxidative stress is considered one of the key mechanisms. Hyperglycemia promotes the accumulation of reactive oxygen species (ROS) and advanced glycation end products (AGEs), exacerbating neuronal damage and Aβ deposition.[19] This process is linked to the increased activity of β-secretase (BACE1), which accelerates the pathological progression of AD. Moreover, hyperglycemia and Aβ synergistically increase oxidative stress, which activates immune responses in the central nervous system, leading to the activation of microglia and astrocytes, thus exacerbating neuroinflammation and neuronal damage.[20] These mechanisms underscore the critical role of glucose management in AD prevention, emphasizing the importance of early intervention.

Based on the global AD burden attributed to HFPG data, females appear to face a higher risk of death. This reflects disparities in access to preventive care for both AD and blood sugar management. This gender disparity in life expectancy is attributed to a combination of biological, social, and environmental factors.[21] Females generally live longer than males and thus have a higher risk of developing chronic and degenerative diseases in later life, which significantly increases death rates and DALYs.[22] AD has a higher incidence in older and postmenopausal females than in males, and estrogen treatment might reduce the risk of AD in these females. In general, estrogens bind to and activate estrogen receptors (ERs)-mediated transcriptional machineries and also stimulate signal transduction through membrane ERs (mERs). Estrogen-related receptors (ERRs), which share homologous sequences with ERs but lack estrogen-binding capabilities, are widely and highly expressed in the human brain and have also been implicated in AD pathogenesis.[23] In public health strategies targeting AD prevention in females, existing research highlights the importance of multilayered interventions. Given the higher prevalence of AD in females, particularly post-menopause, personalized preventive approaches are essential. Scalco and van Reekum et al emphasize the potential role of lifestyle interventions, such as blood pressure control, regular physical activity, and education, in preventing AD.[24] Douthit et al explores the role of counseling, suggesting that social interaction and psychological support could help lower AD risk among females.[25] Additionally, Hussenoeder and Riedel-Heller et al propose advancing a "public brain health" agenda that promotes physical activity, cognitive engagement, and a healthy diet for widespread AD prevention.[26] Barron and Pike et al examine the impact of sex hormones on AD risk in females, noting that decreases in estrogen and testosterone might contribute to AD progression; thus, hormone replacement therapy could offer neuroprotective effects, particularly in postmenopausal females.[27] The female-predominant AD burden necessitates sex-specific screening protocols, such as prioritizing postprandial glucose monitoring in females over 50, along with timely interventions like hormone replacement therapy or exercise-based interventions to reduce the risk of cognitive decline.

The GBD 2021 data highlights significant disparities in the burden of AD and other dementias caused by HFPG across different SDI quintiles. High SDI regions show a higher burden of AD, likely due to a more severe aging population, where age-related diseases are more common. Additionally, advanced healthcare systems in these regions lead to better diagnosis and reporting, resulting in more identified cases.[18] Higher living standards and dietary habits also contribute to a higher incidence of HFPG. In contrast, low and low-middle SDI regions have fewer recorded deaths but wider confidence intervals, indicating higher data uncertainty. These disparities are likely due to limited healthcare resources and insufficient diagnostic and reporting systems, leading to an underestimation of the true burden of AD. Therefore, targeted public health strategies are needed to address aging and HFPG management in high SDI regions, while improving data collection and healthcare services in lower SDI regions to combat AD effectively.[28]

In the frontier analysis, we synthesized global DALY rates trends from 1990 to 2021, alongside SDI data. In high SDI countries, such as the Netherlands and Germany, there is a prevalent trend of increasing effective difference. However, nations like Canada and Iceland exhibit a decreasing trend, signaling advances in health management efficiency. This improvement may stem from enhancements in health systems, bolstered disease prevention, or robust public health strategies. Meanwhile, low SDI countries like the Lao People's Democratic Republic, Timor-Leste, and Papua New Guinea are experiencing an improvement in health management outcomes.

Our combined APC analysis and joinpoint regression reveal significant trends in death rates associated with Alzheimer's disease due to HFPG. Notably, there has been a sharp increase in death rates among individuals aged 85 and above during the 2017–2021 period, underscoring the urgent need for targeted geriatric care and enhanced management strategies for HFPG in this age group. These strategies should encompass various health-related behaviors, including diet, physical activity, medication adherence, medical surveillance, and self-assessment. Effective self-care management of diabetes is particularly important in older adults, as it can help prevent both the long-term complications of diabetes and its associated risk for AD.[29]

Additionally, cohorts born around 1977 show markedly higher death rates, suggesting the need for further research into the unique risk factors affecting these individuals. The Joinpoint analysis also indicates a significant rise in death rates between 1995 and 2000, with a deceleration and possible plateau observed from 2015 to 2021. This slowdown, particularly noticeable among males with a slight decline in AAPCs from 2018 to 2021, may be related to the COVID-19 epidemic that began in 2019. Precise numbers on the prevalence and incidence of stress hyperglycemia during infection

are limited.[30] However, several studies have demonstrated that admission hyperglycemia is associated with an increase in poor outcomes and death in hospitalized patients presenting with an infectious disease.[31,32]

In GBD 2021, the global risk factors associated with Alzheimer's disease were statistically analyzed, including metabolic and behavioral risk factors (high blood glucose, high BMI, tobacco use, smoking).[15] Among these, high blood glucose has the greatest impact on death rates and DALY rates. We employed ARIMA modeling to forecast death rates and DALY rates over the next 15 years, and our predictions indicate a slight decline in both metrics. However, despite this projected decrease, DALY rates remain significantly burdensome. Enhanced public health interventions are imperative to effectively manage HFPG and mitigate its impact on Alzheimer's disease. These interventions should focus on diet, physical activity, medication adherence, and regular medical surveillance. Screening for cognitive impairment in diabetic patients is crucial, as the harm of unrecognized cognitive impairment—such as risks related to diabetes treatment—may be greater than in individuals without diabetes. Screening offers the potential to mitigate these harms, particularly in terms of diabetes treatment risks.[33] Simplifying treatments and tailoring targets can improve compliance and prevent treatment-related complications in patients with impaired cognition. For diabetic patients aged 65 and older, an Endocrine Society Clinical Practice Guideline recommends metformin as the initial oral medication for glycemic management, alongside lifestyle modifications.[34]

Our study demonstrates that while glucose-related biomarkers show potential in identifying cognitive impairment risk, the specificity of our models remains low. One major reason for this is the imbalance in the data, particularly in the classification of cognitive impairment levels, where there are fewer samples of certain cognitive impairment stages. Additionally, the NHANES cognitive function questionnaire employs different scoring methods for cognitive impairment, which may contribute to variability in model performance. In this study, we only used the AFT and DSST to assess cognitive impairment risk, which may have limited the model's ability to distinguish between different levels of cognitive dysfunction. Despite achieving high accuracy (approximately 90.4%), these machine learning models still exhibited some limitations. Future research should focus on addressing data imbalance issues, which could be tackled through techniques such as resampling, weighted loss functions, or the use of generative adversarial networks (GANs).[35,36] These techniques would improve the specificity, stability, and performance of machine learning models in identifying high-risk individuals. The diversity of cognitive impairment scoring methods presents another challenge. Future studies could consider integrating multiple cognitive assessment scales or using standardized scoring systems to enhance the model's generalizability. Additionally, improving model specificity may benefit from the integration of other biomarkers or more refined model parameters. Although studies like those by Ezzati et al[13] and Venugopalan et al[37] demonstrated higher specificity using multimodal data (eg, MRI, genetic data), these methods are not feasible in primary care settings due to their complexity and cost. Therefore, we advocate for the use of readily available physiological markers, such as Insulin level, Random Blood Glucose (RBG), High-sensitivity C-reactive Protein (hs-CRP), to ensure that the model can be widely applied in resource-limited settings. This work paves the way for future studies to explore new biomarkers and modeling techniques that could improve the prediction of AD risk, enhancing early detection and intervention for at-risk populations.

Our study has certain limitations, mainly due to inadequate data systems and significant lags in alternative measurement methods for age-specific and cause-specific death. The COVID-19 pandemic has caused a major health shock globally over the past few years, but these changes have not yet been fully captured in the available data.[38] Although there was no direct attribution of risk to COVID-19, the overall number of deaths and non-fatal outcomes in 2021 were lower than they would have been in the absence of the pandemic. This is likely because COVID-19 accounted for a portion of deaths that would have otherwise occurred due to other causes.[39] Additionally, differences in economic levels between countries could affect healthcare access, quality, and data reliability, potentially influencing HFPG outcomes. Future research should use more rigorous methods, consider economic disparities, and account for pandemic-related disruptions to better understand AD attributable to HFPG.

Conclusion

This study quantifies the global burden of AD attributable to HFPG, highlighting a significant increase in both death rates and DALY rates from 1990 to 2021, particularly among females. The burden was most pronounced in regions with

advanced socio-demographic development, likely due to aging populations and lifestyle factors. Our findings also show that machine learning models, utilizing glucose-related biomarkers, can effectively predict cognitive impairment, with the highest accuracy observed using 2-hour postprandial glucose and FPG. To mitigate the AD burden linked to HFPG, targeted public health strategies focusing on lifestyle modifications and early metabolic screening are essential, particularly in aging populations.

Abbreviations

AAPC, Average Annual Percentage Change; ACF, Autocorrelation Function; AD, Alzheimer's Disease; Aβ, Amyloid-beta; ARIMA, Autoregressive Integrated Moving Average; AUC, Area Under the Curve; APC, Age-Period-Cohort; APS, Average Precision Score; BACE1, Beta-Secretase 1; DALY, Disability-Adjusted Life Years; DSST Digit Symbol Substitution Test; ERs, Estrogen Receptors; ERRs, Estrogen-Related Receptors; F1 Score, A metric for model performance; FNR, False Negative Rate; FPG, Fasting Plasma Glucose; GBD, Global Burden of Disease; GANs, Generative Adversarial Networks; HbA1c, Glycated Hemoglobin; HFPG, High fasting plasma glucose; MCI, Mild Cognitive Impairment; MRI, Magnetic Resonance Imaging; NHANES, National Health and Nutrition Examination Survey; Q-Q, Quantile-Quantile; RBG, Random Blood Glucose; ROS, Reactive Oxygen Species; SDI, Sociodemographic Index; SVM, Support Vector Machines, and hs-CRP, High-Sensitivity C-Reactive Protein.

Data Sharing Statement

The data used in this study are available from the GBD Study (http://ghdx.healthdata.org/) and the NHANES database (https://wwwn.cdc.gov/nchs/nhanes/).

Ethical Approval

This study was approved by the Ethics Committee of Yangzhou University in accordance with the Declaration of Helsinki (approval number: YXYLL-2025 −05). Due to the nature of the secondary data analysis, the review board waived the requirement for informed consent. Additionally, no identifiable personal information was directly analyzed or reported in this research.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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