

ARTICLE

Clinical Research



Androgen deprivation therapy for prostate cancer and neurocognitive disorders: a systematic review and meta-analysis

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BACKGROUND: Prostate cancer is a prevalent disease that urgently needs to address its treatment-related complications. By examining existing evidence on the association between Androgen Deprivation Therapy (ADT) and dementia, this study contributes to the understanding of potential risks. We sought to analyze the currently available evidence regarding the risk of dementia, Alzheimer's disease (AD), vascular dementia, and Parkinson's disease (PD) in patients undergoing ADT.

METHODS: A systematic search of PubMed, EMBASE, Scopus, and Google Scholar was performed to identify studies published from the databases' inception to April 2023. Studies were identified through systematic review to facilitate comparisons between studies with and without some degree of controls for biases affecting distinctions between ADT receivers and non-ADT receivers. This review identified 305 studies, with 28 meeting the inclusion criteria. Heterogeneity was assessed using Higgins I²%. Variables with an I² over 50% were considered heterogeneous and analyzed using a Random-Effects model. Otherwise, a Fixed-Effects model was employed.

RESULTS: A total of 28 studies were included for analysis. Out of these, only 1 study did not report the number of patients. From the remaining 27 studies, there were a total of 2,543,483 patients, including 900,994 with prostate cancer who received ADT, 1,262,905 with prostate cancer who did not receive ADT, and 334,682 patients without prostate cancer who did not receive ADT. This analysis revealed significantly increased Hazard Ratios (HR) of 1.20 [1.11, 1.29], $p < 0.00001$ for dementia, HR 1.26 [1.10, 1.43], $p = 0.0007$ for Alzheimer's Disease, HR 1.66 [1.40, 1.97], $p < 0.00001$ for depression, and HR 1.57 [1.31, 1.88], $p < 0.00001$ for Parkinson's Disease. The risk of vascular dementia was HR 1.30 [0.97, 1.73], $p < 0.00001$.

CONCLUSION: Based on the analysis of the currently available evidence, it suggests that ADT significantly increases the risk of dementia, AD, PD, and depression.

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INTRODUCTION

Prostate cancer is the most common cancer in men and the second deadliest [1]. Approximately 12.9% of men will receive a prostate cancer diagnosis during their lifetime, contributing to a prevalence of 3,343,976 men currently living with the disease in the United States [2]. Treatment ranges from active surveillance to radical prostatectomy, radiotherapy, systemic therapy, and combinations of these [3, 4]. Androgen Deprivation Therapy (ADT) is a widely used treatment for prostate cancer, with approximately half of all patients with prostate cancer estimated to undergo ADT as part of their treatment [5]. This treatment approach encompasses various scenarios, including adjuvant therapy for high-risk patients undergoing radiotherapy for localized disease, locally advanced disease, post-radical prostatectomy in node-positive disease, and metastatic disease [6–10].

Among their various functions, androgens play a crucial role in regulating the growth of prostatic tissue and the growth and

proliferation of cancerous cells [11]. Huggins and Hodges first described ADT in 1941; they won a Nobel Prize in 1967 for their work on ADT in managing symptomatic metastatic prostate cancer [12]. Androgen deprivation can be achieved surgically through bilateral orchiectomy, nearly depleting the body's androgen synthetic capacity, or medically through GnRH/LHRH agonists, decreasing the synthesis of androgens through downstream inhibition or antiandrogens which bind androgen receptors [12].

While the use of ADT is associated with improved outcomes and survival in prostate cancer, it is important to note that it is also linked to significant morbidity. The side effects of ADT encompass a wide range, including osteoporosis, metabolic syndrome, cardiovascular disorders, sexual dysfunction, and cognitive decline [13]. Androgens have been proposed to play a crucial role in the neuronal microenvironment through various mechanisms associated with maintaining synaptic density, degrading beta-amyloid,

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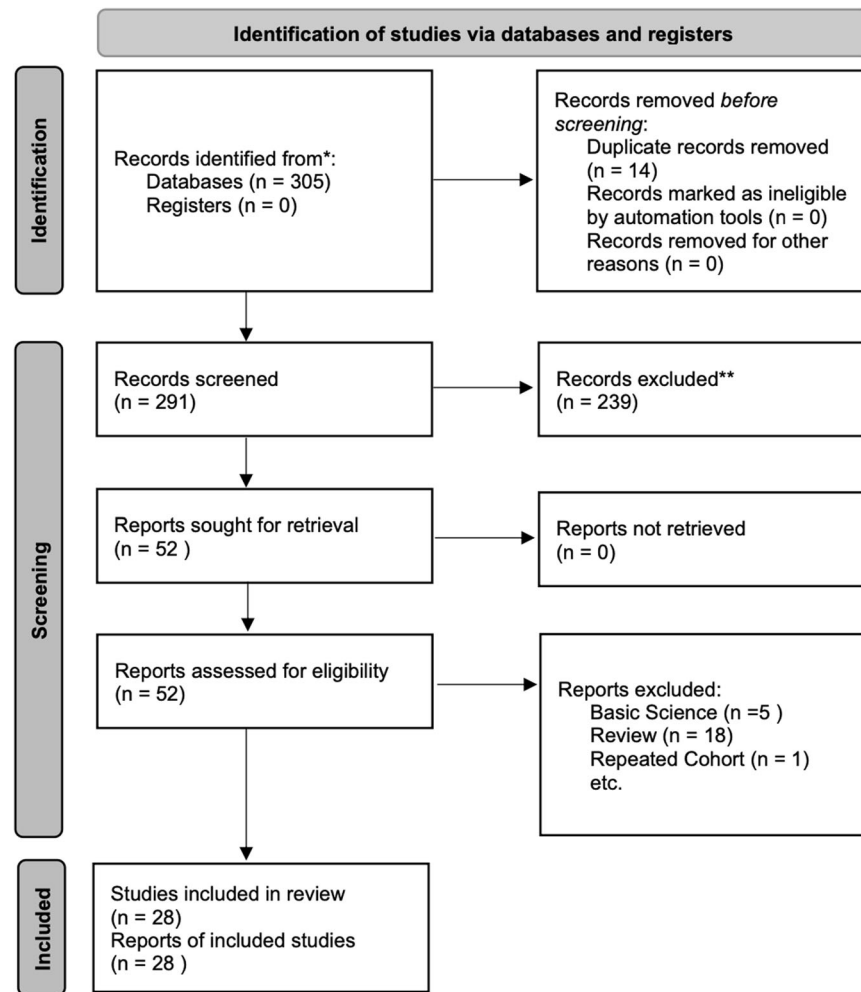


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the selection strategy for eligible studies identification and the inclusion and exclusion process.

and promoting neuronal plasticity [14, 15]. The link between ADT and dementia has been proposed for over 20 years, and recently it has been the subject of epidemiological studies. However, the evidence from these studies has yielded mixed results, indicating a need for further investigation and research in this area [15–17].

This study analyzes the currently available evidence regarding the risk of dementia, Alzheimer's disease (AD), vascular dementia, and Parkinson's disease in patients undergoing Androgen Deprivation Therapy (ADT).

METHODS

In December 2022, with prior PROSPERO registration (CRD42022297904, a systematic search for a systematic review was performed following the PRISMA criteria (Fig. 1). PubMed, EMBASE, Scopus, and Google Scholar were queried for the terms "Androgen Deprivation Therapy", "Prostate Cancer", AND "Dementia", "new onset Dementia", "Alzheimer's Disease" and "Vascular Dementia" in title or abstract. The following search string was employed: "([Prostate Cancer][Title/Abstract] AND ([Androgen Deprivation Therapy][Title/Abstract] OR Orchiectomy [Title/Abstract] OR "Anti-Androgen" [Title/Abstract])) AND (Dementia [Title/Abstract] OR depression [Title/Abstract] OR "Vascular Dementia" [Title/Abstract] OR "Alzheimer's d"" [Title/Abstract] OR Parkinson [Title/Abstract])". No restrictions on publication date were applied; only English, Spanish, and Russian manuscripts were considered. Two independent (DEHG, AZ) reviewers screened returned results for inclusion and data extraction. Data conciliation was performed through consensus. In addition, related articles and a bibliography of identified studies were further screened for possible inclusion. This study was exempt from review by the

institutional review board, and informed consent was not required because data were publicly available.

Study inclusion

Included studies provided a time-dependent analysis confounder adjusted analysis reported in Hazard Ratios (HR) for risk of All-type dementia, Alzheimer's dementia (AD), vascular dementia (VD), Parkinson's disease (PD), and depression in patients with prostate cancer undergoing treatment with androgen deprivation therapy.

Data extraction and analysis

Data was extracted independently by two reviewers (DEHG, AZ). Relevant data for primary and secondary endpoints was HR for All-type dementia, Alzheimer's dementia, vascular dementia, and depression. Further subgroup stratification was performed based on length of ADT duration, type of ADT used - bilateral orchiectomy, GnRH agonists or Antiandrogens, and patient age. Additional subgroup analysis was performed based on the continental distribution of patient populations, excluding overlapping cohorts (i.e., multiple publications using the same database over the same period) and by disease stage.

Data analysis was performed in Review Manager (RevMan) V 5.4.2 (Cochrane). Heterogeneity was assessed using Higgins I^2 %. Variables with over 50% I^2 were considered heterogeneous and were analyzed through a Random-Effects model. Otherwise, a Fixed-Effects model was used. Analysis was performed using the generic Inverse-Variance method, using RevMan's built-in calculator to estimate the logarithmic function and standard error from provided HR and confidence intervals. HR was estimated for studies providing only survival curves but not HR using Tierney's method [18]. Values

are expressed as HR with 95% confidence intervals. *P* values of 0.05 and less were considered statistically significant. Heterogeneity was explored through multiple subgroups and a one-by-one stepwise addition of studies to assess the impact and casuals of heterogeneity. The Newcastle-Ottawa criteria for cohort studies were utilized to perform quality evaluation. Each study was assigned a maximum of 9 points, with 4 points for selection, 2 points for comparability, and 3 points for outcome assessment. Studies with scores ranging from 0 to 3, 4 to 6, and 7 to 9 were classified as low, moderate, and high quality, respectively. Publication bias assessment was visually supported by funnel plots. Primary outcomes were the HRs of dementia and AD. Secondary outcomes were HR of PD, depression, and VD.

Sensitivity analysis for heterogeneity

Subgroup analysis attempting to explore and adjust for variations noted during data extraction was performed further to clarify the impact of these variations in reported results. Subgroups were performed to stratify by ADT received (AA, GnRH Agonists, Orchiectomy), duration of therapy, patient age, and geographical region. Variations in results, when stratified by the characteristics, are narrated in the respective results section. Multiple studies queried the same database with overlapping periods. To adjust for possible duplication of patients, an additional sensitivity analysis was performed, excluding overlapping studies while only retaining the study with the largest population size.

RESULTS

A total of 28 studies were included in the analysis and were retrospective in nature [17, 19–45]. Of these studies, only one did not report the number of patients. Among the remaining 27 studies, there were a total of 2 543 483 patients. Specifically, 900 994 patients had prostate cancer and received ADT, 1 262 905 patients had prostate cancer but did not receive ADT, and 334 682 patients did not have prostate cancer and did not receive ADT. Table 1 provides a summary of the variables analyzed and the quality assessment. Demographic data is summarized in Table 2.

ADT and dementia

The included studies analyzed the risk of various forms of cognitive decline associated with ADT, including dementia, Alzheimer's, and vascular dementia.

Dementia. The risk of dementia was analyzed in a total of 20 studies. The analysis revealed a statistically significant HR of 1.20 [1.11, 1.29], $p < 0.00001$, indicating an increased risk of dementia associated with ADT. Figure 2 displays these findings, and a comprehensive breakdown of the included studies can be found in Supplementary Fig. 1A.

Alzheimer's disease. Thirteen studies were included in the analysis of the risk of developing AD. The analysis of these studies concluded a statistically significant risk with a HR of 1.26 [1.10, 1.43], $p < 0.00001$, indicating an increased risk of AD in patients undergoing ADT. These findings are visually displayed in Fig. 2, and a detailed breakdown of the included studies can be found in Supplementary Fig. 1B.

Vascular dementia. The risk of vascular dementia was assessed in 3 studies. The pooled analysis of these studies indicated a non-significant risk with a HR of 1.30 [0.97, 1.73], $p < 0.00001$. These findings are depicted in Fig. 2, and a comprehensive breakdown of the included studies can be found in Supplementary Fig. 2B.

Depression

The development of depression related to ADT was analyzed in a total of 7 studies. The analysis of these studies revealed a significant risk of depression in patients undergoing ADT, with a HR of 1.66 [1.40, 1.97], $p < 0.00001$. These findings are visually presented in Fig. 2, and a detailed breakdown of the included studies can be found in Supplementary Fig. 2A. Table 2

provides a summary of the diagnostic criteria for depression for each study.

Parkinson's disease

The association between Parkinson's Disease and ADT was examined in 3 studies, and the pooled analysis demonstrated a significantly increased risk with a HR of 1.57 [1.31, 1.88], $p < 0.00001$. These findings are presented in Fig. 2, and a comprehensive breakdown of the included studies can be found in Supplementary Fig. 2C.

ADT modality and dementia

A subgroup analysis was conducted to stratify the risk of dementia or Alzheimer's disease (AD) based on different modalities of ADT, including orchiectomy, GnRH agonists/antagonists, and antiandrogens.

Dementia. The three therapies above, including bilateral orchiectomy, GnRH agonists/antagonists, and antiandrogens, were analyzed, and significant increases in risk were observed for all three forms of therapy. Among them, the highest risk was associated with bilateral orchiectomy, with a HR of 1.36 [1.17, 1.59], $p < 0.0001$. It is important to note that this subgroup had the lowest number of included studies (three). These findings are presented in Fig. 3, and a detailed breakdown of the included studies can be found in Supplementary Fig. 3A.

Alzheimer's disease. The analysis of various individual ADT modalities and the risk of AD indicates that orchiectomy and antiandrogens are associated with a significantly increased risk. These findings are depicted in Fig. 4, and a comprehensive breakdown of the included studies can be found in Supplementary Fig. 3B.

Treatment duration

Studies that provided risk stratification based on treatment duration were included to analyze the impact of duration on the risk of ADT.

Dementia. Both therapies lasting less than 6–12 months and those lasting more than 6–12 months were associated with a significantly increased risk of dementia. However, the risk was higher in longer duration therapy, with a HR of 1.22 [1.10, 1.36], $p < 0.0001$. These findings are visually presented in Fig. 3, and a comprehensive breakdown of the included studies can be found in Supplementary Fig. 4A.

Alzheimer's disease. The analysis of treatment duration and the risk of developing Alzheimer's disease (AD) indicated an increased risk regardless of the duration of treatment. These findings are presented in Fig. 4, and a detailed breakdown of the included studies can be found in Supplementary Fig. 4B.

Age, ADT, and dementia

Among the analyzed studies, only three examined subsets of patients based on age at initiation of ADT. In patients younger than 65, no significant risks were found. However, a significant risk was observed in patients aged 65 and older with a HR of 1.76 [1.30, 2.37], $p = 0.0002$. These findings are depicted in Fig. 3, and a comprehensive breakdown of the included studies can be found in Supplementary Fig. 5A.

The same two studies analyzed age subgroups and AD; however, in this case, the pooled analysis suggested an increased risk for AD regardless of age. These findings are displayed in Fig. 4 with a full breakdown of included studies in Supplementary Fig. 5B.

Regional analysis

A subgroup analysis was conducted based on the continental geographic regions of the included cohorts.

Table 1. Displays key summary data from included studies on population size, data origin, ADT employed, key findings, and quality rating.

Author	Year	Country	Cohort Years	Database	Total Size	ADT	Non-ADT	NC	ADT Type	Medications	Dementia	AD	Vascular Dementia	PD	Depression	NOS Score
Ng	2018	Australia	2004–2010	Pharmaceutical Benefits Scheme	3689	NR	NR	NA	GnRH Agonists	Goserelin Leuprolide Triptorelin	NA	=	NA	NA	+	7
									Antiandrogens	Bicalutamide Cyproterone Flutamide Nilutamide						
Kim	2021	Korea	2008–2017	Health Insurance Review and Assessment Service (HIRA)	44,854	22,427	22,427	NA	GnRH Agonists	NR	+	+	+	NA	NA	8
									Antiandrogens	NR						
Shim	2020	Korea	2012–2016	National Health Insurance Service	6429	3201	3228	NA	GnRH Agonists	Goserelin Leuprolide Triptorelin	+	NA	NA	=	NA	7
									GnRH Agonists	Goserelin Leuprolide Triptorelin	+			NA	NA	
Tae	2019	Korea	2008–2015	National Health Insurance Service	25,332	12,620	12,712	NA	GnRH Agonists	Goserelin Leuprolide Triptorelin	+			NA	NA	8
									Antiandrogens	Bicalutamide Cyproterone Flutamide			NA			
Kang	2020	Korea	2007–2013	National Health Insurance Service	260,910	51,251	NA	209,659	NR	NR	+	+	+	NA	NA	8
									Bilateral Orchiectomy	NA						
Robinson	2019	Sweden	2006–	Prostate Cancer Database Sweden	146,985	18,758	7209	121,018	GnRH Agonists	NR	+	+				7
									Antiandrogens	NR			NA	NA	NA	
Huang	2020	Taiwan	2008–2015	Taiwan Cancer Registry	23,651	16,747	6904	NA	Bilateral Orchiectomy	NA						7
									GnRH Agonists	Leuprolide Goserelin Triptorelin Buserelin	+	+	NA	NA	NA	
Hong	2020	Taiwan	2000–2008	Longitudinal Health Insurance Database for Catastrophic Illness Patients	17,425	12,740	4685	NA	Antiandrogens	Bicalutamide Cyproterone Flutamide						8
									Bilateral Orchiectomy	NA						
Kao	2017	Taiwan	2001–2008	Taiwan National Health Insurance Research Database	1314	755	559	NA	GnRH Agonists	Goserelin Leuprolide Triptorelin	=	NA	NA	NA	NA	6
									Antiandrogens	Bicalutamide Cyproterone Flutamide Nilutamide						
Liu	2021	Taiwan	2002–2016	Taiwan National Health Insurance Research Database	17,486	8743	8743	NA	GnRH Agonists	Leuprolide Goserelin Triptorelin Buserelin	=	NA	NA	NA	NA	8
									Antiandrogens	Bicalutamide Cyproterone						

Table 1. continued

Author	Year	Country	Cohort Years	Database	Total Size	ADT	Non-ADT	NC	ADT Type	Medications	Dementia	AD	Vascular Dementia	PD	Depression	NOS Score
Chung	2016	Taiwan	2001–2008	Longitudinal Health Insurance Database	1335	768	567	4005	Bilateral Orchiectomy	Flutamide Nilutamide	NA	=	NA	=	NA	6
									GnRH Agonists	NR						
Jhan	2017	Taiwan	2000–2009	Taiwan National Health Insurance Research Database	24,360	15,959	8401	NA	Antiandrogens	NR	NA	+	NA	NA	NA	8
									GnRH Agonists	Goserelin Leuprolide Triptorelin						
Liu	2021	UK	1998–2018	The Health Improvement Network (THIN)	29,898	14,949	14,949	NA	Antiandrogens	Bicalutamide Cyproterone Flutamide Nilutamide	=	NA	NA	NA	NA	8
									GnRH Agonists	Leuprolide Goserelin Triptorelin Buserelin						
Khosrow-Khavar	2017	UK	1988–2015	Clinical Practice Research Datalink	30,903	15,310	15,593	NA	Bilateral Orchiectomy	NA	=	NA	NA	NA	NA	8
									GnRH Agonists	Leuprolide Goserelin Triptorelin Buserelin						
Tully	2021	USA	2007–2014	TRICARE	9117	8792	325	NA	Antiandrogens	Bicalutamide Cyproterone Flutamide Nilutamide	=	NA	NA	NA	+	8
									GnRH Agonists	NR						
Balk	2017	USA	2001–2014	Medicare Claims	1,238,879	440,129	798,750	NA	Antiandrogens	NR	+	–	NA	NA	NA	8
									GnRH Agonists	NR						
Deka	2018	USA	2001–2015	US Department of Veterans Affairs Jayadevappa	45,218	NR	NR	NA	Antiandrogens	NR	=	=	=	NA	NA	6
									GnRH Agonists	NR						
NA	NA	NA	8	Bilateral Orchiectomy	NA	NA	NA	NA	Antiandrogens	NR	=	NA	NA	NA	NA	NR
									GnRH Agonists	Surveillance, Epidemiology and End Results - Medicare						
Nead	2015	USA	Stanford: 1994–2013 Mt. Sinai 2000–2013	Stanford + Mt Sinai	16,888	2397	14,491	NA	Antiandrogens	Leuprolide Goserelin Triptorelin Buserelin Histrelin Degarelix	NA	+	NA	NA	NA	8
									GnRH Agonists	Bicalutamide Cyproterone Flutamide Enzalutamide						
Nead	2016	USA	1994–2013	Stanford	3652	1826	1826	NA	Antiandrogens	Leuprolide Goserelin Triptorelin Buserelin Histrelin Degarelix	+	NA	NA	NA	NA	8
									GnRH Agonists	Leuprolide Goserelin Triptorelin Buserelin Histrelin Degarelix						

Table 1. continued

Author	Year	Country	Cohort Years	Database	Total Size	ADT	Non-ADT	NC	ADT Type	Medications	Dementia	AD	Vascular Dementia	PD	Depression	NOS Score
Loneragan	2021	USA	1995–2017	CaPSURE	8506	4253	4253	NA	GnRH Agonists	Bicalutamide Cyproterone Flutamide Enzalutamide	+	NA	NA	NA	NA	8
Krasnova	2019	USA	1992–2009	Surveillance, Epidemiology and End Results - Medicare	100,414	37,911	62,503	NA	NR	NR	+	+	NA	NA	NA	8
Nguyen	2018	USA	1992–2009	Surveillance, Epidemiology and End Results - Medicare	201,797	94,528	107,269	NA	GnRH	Leuprolide Goserelin Triptorelin Degarelix	+	NA	NA	NA	NA	8
Dinh	2016	USA	1992–2006	Surveillance, Epidemiology and End Results - Medicare	78,552	33,882	44,670	NA	GnRH Agonists	NR	NA	NA	NA	NA	+	8
Chung	2017	Taiwan	2001–2010	Taiwan National Health Insurance Research Database	1714	868	846	NA	GnRH Agonists	NR	NA	NA	NA	NA	+	8
Alonso-Quinones	2021	USA	2004–	The Mayo Clinic Study on Aging	241	67	174	NA	GnRH Agonists	NR	NA	NA	NA	NA	=	7
Crump	2023	Sweden	1998–2017	National Prostate Cancer Register	NR	NR	NR	NA	Bilateral Orchiectomy	NR	NA	NA	NA	NA	NA	7
Deka	2019	USA	2001–2015	Veterans Affairs Corporate Data Warehouse	39,965	14,843	25,122	NA	GnRH Agonists	Leuprolide Goserelin Triptorelin Histrelin Degarelix	NA	NA	NA	NA	+	8
Kim	2022	Korea	2006–2013	Korean National Health Insurance System of Statistics	9880	4940	4940	NA	Antandrogens	Bicalutamide Flutamide Nilutamide	=	NA	NA	NA	NA	8

ADT Androgen Deprivation Therapy, NOS Newcastle-Ottawa Scale, NR not reported, NA non applicable, + increased risk, = same risk, – lower risk.

Table 2. Displays key summary data from included studies on demographic characteristics and depression diagnostic criteria.

Author	Year	Country	Mean Age (SD) – ADT	Race – ADT	Comorbidities – ADT	PcA Stage or risk category – ADT	Depression Diagnostic Criteria
Ng	2018	Australia	NR	NR	NR	NR	Rx-Risk-V model was employed using medication dispensing records as surrogate for the diagnosis
Kim	2021	Korea	71.16 (7.83)	NR	CVD: 20.6% COPD: 10.4% HTN: 36.6% Stroke: 8.2% HLD: 37.1%	NR	NA
Shim	2020	Korea	72.8 (8.5)	NR	CVD: 20.9% COPD: 9.1% HTN: 50.2% HLD: 20.2%	NR	NA
Tae	2019	Korea	71.2 (8.2)	NR	HTN: 47.1% DM: 21.5% PVD: 6.8% MI: 1.1%	NR	NA
Kang	2020	Korea	68.5 (8.4)	NR	HTN: 51.0% DM: 18.2% HLD: 23.2%	NR	NA
Robinso	2019	Sweden	76.5 (7.6)	NR	NR	Low: 13.2% Intermediate: 28.6% High: 40.9	NA
Huang	2020	Taiwan	GnRH: 72 (66–79) ^a Orchiectomy: 73 (66–79) ^a Antiandrogen: 73 (66–79) ^a	NR	b	b	NA
Hong	2020	Taiwan	74.1 (7.89)	NR	CVD: 23.7% HTN: 66.0% HLD: 29.5% DM: 25.0%	NR	NA
Kao	2017	Taiwan	74.2 (7.9)	NR	NR	NR	NA
Liu	2021	Taiwan	70.3 (8.9)	NR	HTN: 52.6% DM: 20.6% Stroke: 9.7% COPD: 12.4%	NR	NA
Chung	2016	Taiwan	74.2 (8.0)	NR	HTN: 68.1% DM: 27.3% Stroke: 31.3% HLD: 35.7%	NR	NA
Jhan	2017	Taiwan	75.48 (6.92)	NR	HTN: 16.4% Stroke: 4.3% HLD: 1.6% DM: 4.7%	NR	NA
Liu	2021	UK	70.0 (8.5)	NR	HTN: 39.8% DM: 10.0% Stroke: 3.4% COPD: 5.5%	NR	NA
Khosrow-Khavar	2017	UK	72.8 (8.3)	NR	NR	NR	NA
Tully	2021	USA	NR	NR	NR	NR	One inpatient or two outpatient diagnoses were considered clinically depressed.

Table 2. continued

Author	Year	Country	Mean Age (SD) – ADT	Mean Age (SD) – Non-ADT	Race - ADT	Comorbidities – ADT	PCa Stage or risk category - ADT	Depression Diagnostic Criteria
Baik	2017	USA	76.36 ^c	74.57 ^c	White: 84.07% Black: 9.46% Hispanic: 4.08% Asian: 1.49% Other: 0.90%	COPD: 17.8% HTN: 65.5% HLD: 55.7% DM: 24.9%	NR	NA
Deka	2018	USA	NR	NR	NR	NR	NR	NA
Jayadevappa	2019	USA	75.2 (5.9)	75.2 (6.4)	White: 76.7% Black: 10.9% Hispanic: 6.7% Other: 6.7%	NR	Well differentiated: 4.8% Moderately differentiated: 63.0% Poorly differentiated: 25.1% Unknown: 7.1%	NA
Nead	2015	USA	70.9 (10.8)	70.9 (12.6)	NR	DM: 21.0% Malignancy: 7.0%	NR	NA
Nead	2016	USA	69.9 (11.0)	69.8 (11.3)	NR	CVD: 26.8% DM: 20.2% Stroke: 1.2	NR	NA
Lonerga	2021	USA	NR	NR	NR	NR	NR	NA
Krasnova	2019	USA	75 (71–79) ^a	72 (69–76) ^a	White: 83.0% Black: 10.2% Other: 6.7%	NR	cT1: 41.8% cT2: 52.5% cT3–cT4: 5.7%	NA
Nguyen	2018	USA	NR	NR	Non-Hispanic White: 77.5% Non-Hispanic Black: 12.0% Hispanic: 5.8% Other: 4.7%	NR	I: 19.4% II: 30.5% III: 2.4% IV: 10.7%	NA
Dinh	2016	USA	75.7 ^c	73.5 ^c	NR	NR	NR	ICD-9 codes for Major depressive disorder, initial diagnosis; Major depressive disorder, recurrent; Depression associated with bipolar I disorder; Depressive psychoses; Depression associated with personality disorder; Adjustment disorder with depression; Depressive disorder, not elsewhere classified.
Chung	2017	Taiwan	74.1 (8.4)	70.4 (10.8)	NR	HTN: 71.2% DM: 28.7% HLD: 38.5% Stroke: 32.8%	NR	Presence of depressive disorder codes in inpatient claims data.
Alonso-Quinones	2021	USA	78 (70–90) ^a	ADT Use < 5 years: 78 (72–87) ^a ADT use ≥ 5 years: 82 (71–90) ^a	NR	NR	NR	Score of 13 or greater on the Beck Depression Inventory

Table 2. continued

Author	Year	Country	Mean Age (SD) – ADT	Mean Age (SD) – Non-ADT	Race – ADT	Comorbidities – ADT	PCa Stage or risk category – ADT	Depression Diagnostic Criteria
Crump	2023	Sweden	NR	NR	NR	NR	NR	ICD-10 codes F32–F33 in the Swedish In-Patient and Out-Patient Registers and primary care records
Deka	2019	USA	67.97 ^a	66.24 ^a	White: 67.06% Black: 29.50% Other: 3.45%	NR	cT1: 55.58% cT2:38.13% cT3: 5.01%	ICD-9 codes: 296.2, 296.3, 296.5, 296.6, 296.7, 298.0, 301.10, 301.12, 301.13, 309.0, 309.1, and 311.
Kim	2022	Korea	NR	NR	NR	HTN: 49.6% DM: 25.8% CVD: 9.3%	NR	NA

ADT Androgen Deprivation Therapy, HTN hypertension, DM diabetes mellitus, CVD cardiovascular disease, HLD hyperlipidemia, COPD chronic obstructive pulmonary disease, MI myocardial infarction, NR not reported, NA not applicable.

^aMedian (IQR).

^bStratified by type of therapy.

^cSD not reported.

Dementia. The geographical subgroup analysis revealed that only cohorts from America showed an increased risk of dementia with ADT, with a HR of 1.19 [1.08, 1.31], $p < 0.0001$. These findings are visually presented in Fig. 5, and a comprehensive breakdown of the included studies can be found in Supplementary Fig. 6A.

Alzheimer's disease. Geographical subgroup analysis revealed that American and Asian cohorts had an increased risk of dementia with ADT, with HR of 1.13 [1.00, 1.27], $p < 0.00001$ and 1.23 [1.05, 1.46], $p = 0.01$, respectively. These findings are displayed in Fig. 6, and a comprehensive breakdown of the included studies can be found in Supplementary Fig. 6B.

Sensitivity analysis suggests that, for the American subgroup, the main drivers of heterogeneity were Nead et al. Baik et al. and Deka et al. However, these studies did not significantly alter the results and exhibited high interstudy heterogeneity. Robinson et al. were the main drivers of heterogeneity in the European cohort. Partial exclusion of the antiandrogen and orchiectomy subgroups significantly increased risk, while the full exclusion of Robinson et al.'s cohort resulted in non-significant differences. In the Asian region, Kang was the main driver of heterogeneity, and its exclusion did not significantly alter the results.

In the geographical analysis of AD, Baik was identified as the main driver of heterogeneity for the American cohorts. However, excluding Baik did not significantly alter the results. In the Asian cohorts, Jhan and Kang et al. were identified as the main drivers of heterogeneity, but excluding them did not affect the results.

Localized and adjusted disease

Ten studies were included for analysis, which consisted of populations featuring only patients with localized prostate cancer or whose propensity scoring successfully adjusted for disease stage. The overall Hazard Ratio (HR) for dementia was 1.23 [1.03–1.38], with a $p = 0.0009$.

Overlapping databases

The included studies examined large institutions such as Surveillance Epidemiology and End Results (SEER) and the Korean Health Insurance Information Service (KHIS). Therefore, there may be overlap in the analyzed populations across these studies. Upon excluding the overlapping studies, the HR was determined to be 1.15 [1.07, 1.24], $p = 0.0002$.

Risk of bias assessment

We evaluated all 28 studies thoroughly. In the study by Liu et al. two distinct cohorts were considered separately during the Risk of Bias assessment, resulting in a total of 29 studies analyzed. Our assessment of the risk of bias revealed that 27 out of these 29 trials received scores ranging from 7 to 8, signifying a low risk of bias. However, 2 trials, specifically those conducted by Deka et al. and Chung et al. received a score of 6, indicating a moderate risk of bias. The funnel plots are presented in Supplementary Fig. 7.

DISCUSSION

This meta-analysis presents the results of 28 analyzed studies. The findings suggest an increased risk of dementia, Alzheimer's disease (AD), Parkinson's disease (PD), and depression in patients undergoing androgen deprivation therapy (ADT) for prostate cancer. All analyzed treatment modalities showed an increased risk of dementia. Orchiectomy had the highest estimated risk; however, it is important to note that this treatment modality also had the least evidence. Furthermore, the employed methodology does not differentiate whether there are statistical differences between different types of ADT. Future studies should incorporate comparisons of treatment modalities into the results using network analysis or similar approaches.

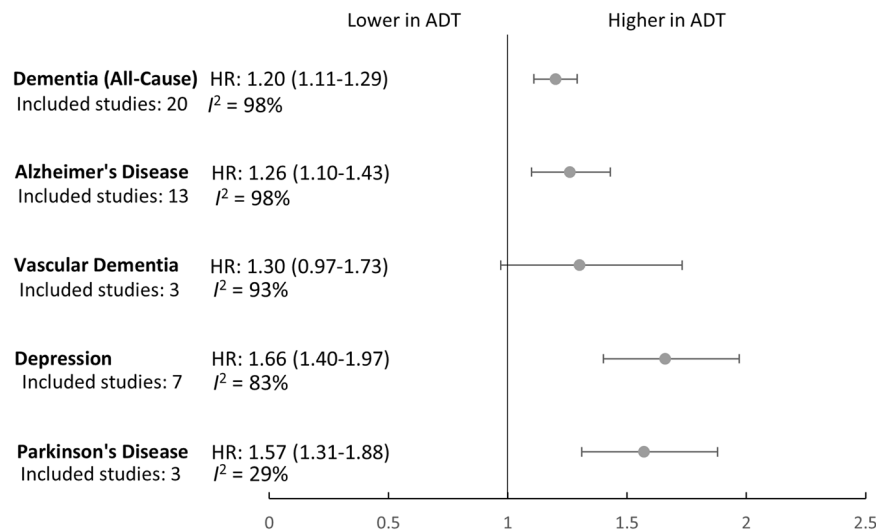


Fig. 2 Displays a summary forest plot with Hazard Ratios for key primary outcomes: Dementia (All-Cause), Alzheimer's, Vascular Dementia, Depression, and Parkinson's Disease. ADT Androgen deprivation therapy, HR Hazard ratio, I^2 Heterogeneity.

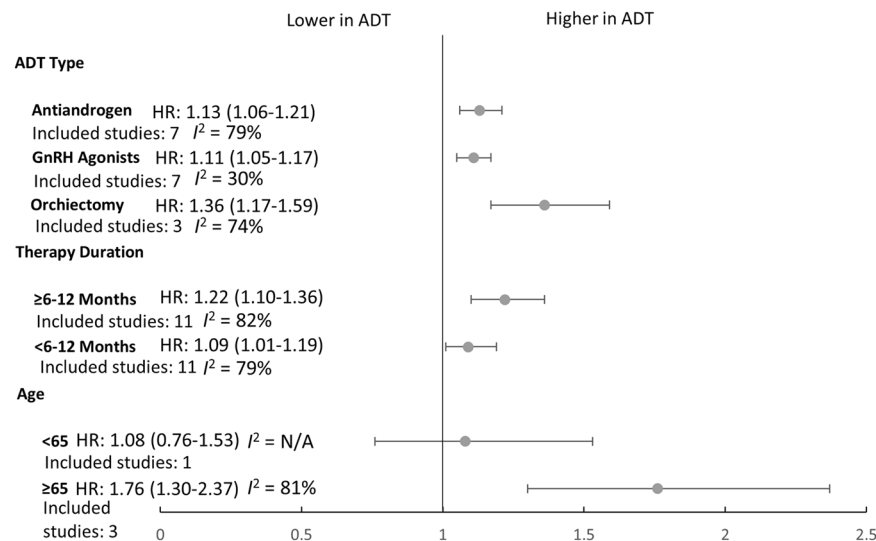


Fig. 3 Displays summary forest plot with Hazard Ratios for subgroup analysis of dementia stratified by androgen deprivation therapy type, duration, and patient age. ADT Androgen deprivation therapy, HR Hazard ratio, I^2 Heterogeneity.

Three included studies incorporated non-cancer cohorts into their analysis. These studies did not identify any significant differences in the risk of dementia between patients with prostate cancer not undergoing androgen deprivation therapy (ADT) and matched non-cancer cohorts. This finding strengthens the belief that ADT is the cause, rather than a confounder, of the established increased risk of various cognitive and neurodegenerative conditions observed in this analysis. This conclusion is further supported by prior evidence showing the influence of androgens on neuronal sustenance and plasticity [14, 15]. A meta-analysis by Lv et al. found that cohorts with low testosterone levels are at an increased risk of developing dementia [46]. Other studies have linked decreased bioavailability of testosterone in older men with dementia [47].

The duration of treatment was found to increase the risk of dementia and AD. Although the risk appears to be higher with longer durations of ADT, the current methodology does not precisely quantify the differences or increases in risk. Previous studies have already established a connection between prolonged ADT and an increased risk of dementia [17, 23, 28, 30–37, 39, 40].

Conversely, the age at which ADT is initiated may influence a patient's susceptibility to dementia. Only two studies showed that patients under 65 do not appear to be at an increased risk of dementia compared to those older than 65. However, when analyzing the relationship between age and AD, our analysis suggests an increased risk regardless of age. It is important to note that these findings are derived from limited evidence, and further studies would be beneficial to provide more comprehensive insights.

Race and socioeconomic factors have significantly impacted populations' risk of neurocognitive decline [48, 49]. Regional analysis revealed that studies from American cohorts were the main contributors to the significant differences in risk observed, with increased risk of dementia in patients undergoing ADT. On the other hand, European studies did not show a significant increase in dementia risk associated with ADT. In terms of AD, both American and Asian cohorts showed an increased risk. It is worth noting that genetic and environmental factors may play a role in modifying the risk of cognitive decline in patients with prostate cancer. However, it is important to consider that the

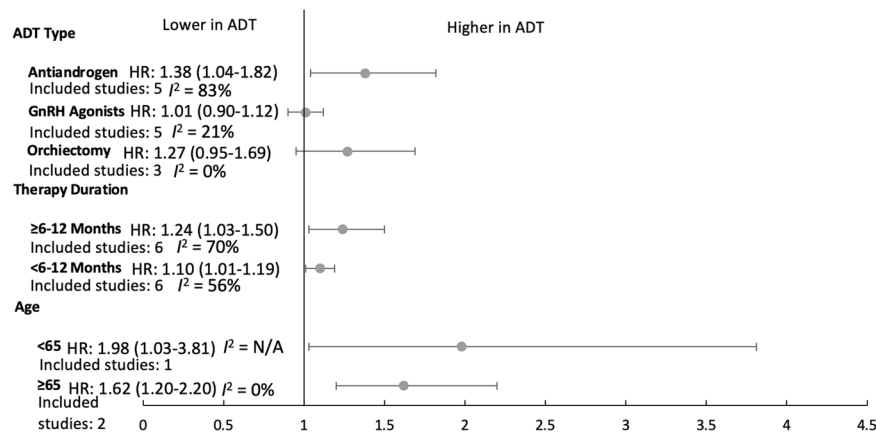


Fig. 4 Displays summary forest plot with Hazard Ratios for subgroup analysis of Alzheimer's Disease stratified by androgen deprivation therapy type, duration, and patient age. ADT Androgen deprivation therapy, HR Hazard ratio, I^2 Heterogeneity, N/A Not applicable.

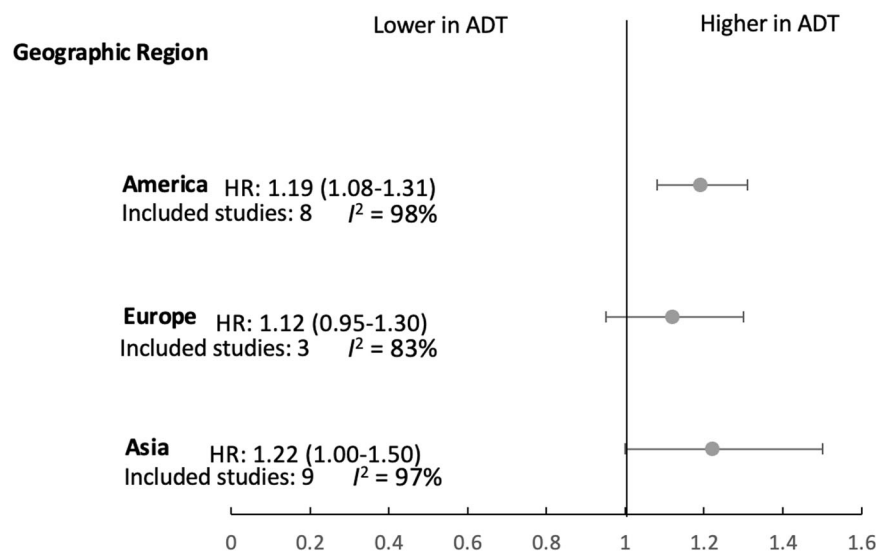


Fig. 5 Displays summary forest plot with Hazard Ratios for subgroup analysis of dementia stratified by geographic region of analyzed population. ADT Androgen deprivation therapy, HR Hazard ratio, I^2 Heterogeneity.

variations in risk observed could also stem from differences in the risk modeling, given that these studies utilized propensity matching. Furthermore, the diversity within some of the included databases limits the ability of regional analysis to discriminate between race-related risks adequately.

Disease severity and stage could also influence the risk of cognitive decline, either through additional treatments employed or through inherent biological processes [50]. Additional treatments such as chemotherapy have also been previously established to increase the risk of dementia [51]. Although additional studies have found conflicting evidence on the possible relationship between cancer and cognitive decline [52].

This study faces various limitations. Methodological variation between included studies, as well as unaccounted confounders in the different regions, races, and ethnicities included, may impact results. Additionally, propensity matching algorithms are prone to interstudy variation and thus adjustment of confounders might be unequal. The high heterogeneity observed even within subgroups suggests the presence of other factors influencing the results. Although subgroup analysis provides additional insights, it does not allow for quantitative analysis of observed differences. More precise methods, such as meta-regression or network comparison of different interventions,

would be beneficial in quantifying the variations in risk. Another limitation is that the included studies also had variations in clinical stage and treatment employed, which could be potential confounders that were not adequately accounted for. However, sub-analysis focusing on localized prostate cancer patients still showed significant results. Furthermore, including studies with stratified data by type of ADT may introduce bias due to the particular offering of certain ADT types based on disease stage.

CONCLUSION

Available evidence suggests that ADT significantly increases the risk of dementia, AD, PD, and depression. The increased risk of dementia is observed regardless of the treatment modality and duration; however, quantitative analysis is needed to assess the differences between treatment modalities and durations accurately. It is important to note that some studies may have used similar databases and overlapping patient cohorts, which could introduce potential bias or duplicate data in this analysis. Clinicians should be vigilant in monitoring prostate cancer patients undergoing ADT for symptoms of cognitive decline and other neurodegenerative disorders.

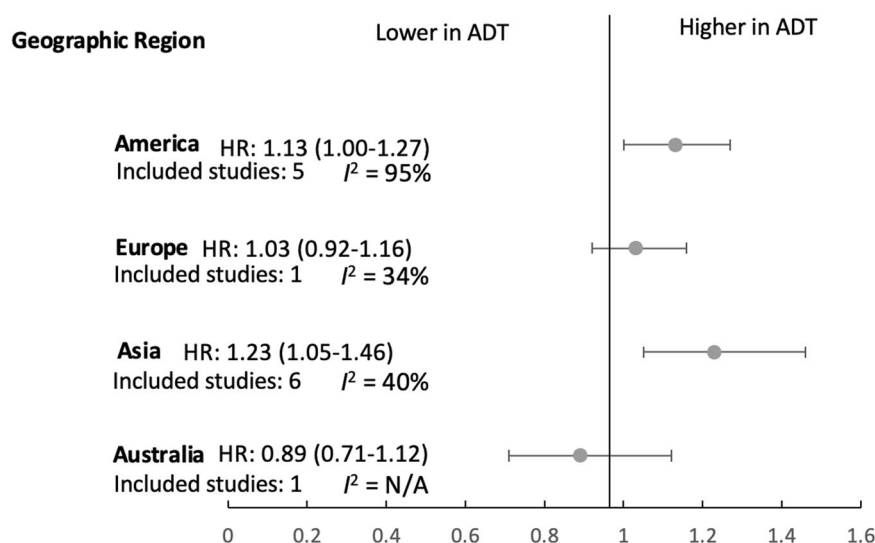


Fig. 6 Displays summary forest plot with Hazard Ratios for subgroup analysis of Alzheimer's Disease stratified by geographic region of analyzed population. ADT Androgen deprivation therapy, HR Hazard ratio, I² Heterogeneity, N/A Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, DEH, upon reasonable request.

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COMPETING INTERESTS

M.K is a consultant for AbbVie, Marius, Tolmar, Endo, Petros, Boston Scientific, Coloplast, Halozyme and an Investor in Sprout. The rest of the authors have nothing to disclose.

ADDITIONAL INFORMATION

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