Supportive Care in Cancer (2024) 32:561
https://doi.org/10.1007/s00520-024-08753-3

REVIEW

Risks associated with cognitive function and management strategies in the clinical use of ADT: a systematic review from clinical and preclinical studies

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Received: 17 January 2024 / Accepted: 20 July 2024 / Published online: 31 July 2024

Abstract

Prostate cancer is one of the most common malignancies and a leading cause of death in men. Owing to its excellent antitumor effects, androgen deprivation therapy (ADT) is widely used in the treatment of prostate cancer. However, its use is controversial because of its potential for inducing cognitive decline. In this review, we summarized the findings of preclinical and clinical studies investigating the effects of ADT on cognitive function in prostate cancer. We discussed the methods used to assess cognitive function in these studies, elucidated the mechanisms through which ADT affects cognitive function, and highlighted recent advancements in cognitive assessment methods. The findings of this review serve as a valuable reference for examining the relationship between ADT and cognitive function in future studies. Besides, the findings may help clinicians understand the advantages and disadvantages of ADT and optimize the treatment plan so as to minimize the adverse effects of ADT.

Keywords ADT · Prostate cancer · Cognitive function · Androgens

Introduction

Prostate cancer is the second most common cancer, following lung cancer, among adult men worldwide. In 2020, more than 1.41 million new cases of prostate cancer were reported, with an incidence rate of 7.3% [1]. Because prostate cancer is mostly asymptomatic in its early stages, the optimal time for treatment is frequently missed, leading to a high mortality rate [2]. Prostate cancer imposes a substantial socioeconomic burden and is a major challenge to the allocation of healthcare resources [3]. Because both progression and metastasis of prostate cancer are driven by androgens [4], androgen deprivation therapy (ADT) is considered the mainstay of treatment for prostate cancer. ADT works by suppressing androgens or inhibiting their production (serum testosterone < 50 ng/dL or 1.735 nmol/L) [5]. Over the past decades, ADT has demonstrated excellent therapeutic effects against prostate cancer, and significant advancements have been made in drug-based denervation therapy [6, 7]. At present, ADT is considered the cornerstone of treatment for metastatic prostate cancer [8]. The side effects of ADT include bone and joint pain [9], impaired sexual function, and an increased risk of cardiovascular disease and cognitive decline. Although ADT is initially effective, patients may eventually develop castration-resistant prostate cancer [10–13]. Moreover, recent studies have reported that ADT increases the risk of cognitive decline in patients with prostate cancer. Cognitive decline is a relatively slow-paced condition characterized by diminished performance in domains such as attention, executive function, and memory [14, 15]. Alibhai et al. conducted a 3-year follow-up study on patients with prostate cancer who underwent ADT and found that ADT was not associated with cognitive decline in these patients [16]. However, several large-sample studies have reported that ADT leads to a significant increase in the risk of cognitive decline [17–19]. Therefore, the utilization of ADT may exacerbate cognitive decline in patients with

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dementia and Alzheimer's disease, and this high-risk treatment behavior cannot be overlooked [20, 21]. In this review, we summarized the findings of preclinical and observational clinical studies investigating the effects of ADT on cognitive function. The findings and methodologies of the two types of studies were qualitatively analyzed to explain the inconsistencies in findings. Altogether, this review improves the understanding of the relationship between ADT and cognitive function and serves as a valuable reference for designing and conducting future studies focusing on the effects of ADT on cognitive function.

Methods

Aim and research design

This present work is a systematic review including clinical and preclinical studies using ADT therapy, cognitive function, and cognitive impairment as keywords, with the aim of qualitatively analyzing whether the use of ADT increases the risk of cognitive decline in prostate cancer patients. A concise meta-analysis was conducted to determine the impact of ADT on cognitive function in clinical trials. This review can provide support for managing the risk of cognitive decline in clinic patients with prostate cancer undergoing ADT therapy.

Search strategy

A comprehensive literature search was performed in the PubMed/Medline, Embase, Web of Science, and Cochrane databases to screen for eligible articles on ADT and cognitive function published from the date of database inception to June 28, 2023, with no restrictions on language. The literature search was conducted using the following keywords: "androgen," "deprivation," "therapy," "cognitive," "prostate," "cancer," "mouse," and "rat." The search strategy was formulated to select observational clinical studies and experimental animal studies. This review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22].

Study selection

Clinical studies

The inclusion criteria for clinical studies were as follows: (1) study participants should include patients with prostate cancer who underwent ADT; (2) the study should include a detailed description of the methods used to assess cognitive function; (3) the study should involve one or multiple follow-ups in addition to baseline assessment; (4) the study should report detailed data on the level of cognitive function of patients.

The following types of articles were excluded: (1) duplicate publications; (2) reviews, conference abstracts, pathology reports, and animal experiments; (3) studies based on the analysis of patient data from electronic databases; (4) retrospective or cross-sectional studies that lacked a follow-up; (5) pilot studies or a qualitative research design.

Preclinical studies

The inclusion criteria for preclinical studies were as follows: (1) the animal species used in the study should be male mice or rats; (2) the characteristics of experimental animal species should be comprehensively described; (3) the method of castration of mice or rats should be comprehensively described; (4) the primary endpoint should be cognitive function. The following types of articles were excluded: (1) duplicated studies; (2) reviews, conference abstracts, and case reports; (3) clinical studies or studies that did not involve animal experiments.

Data extraction

Data were extracted from each study by three researchers independently (Mengfan Cui, Liming Chen, and Shimin Liu). The three researchers assessed the eligibility of studies based on the abovementioned criteria, and any disagreements were resolved by reaching a consensus. All data collected from the included studies are mentioned in Table 1.

Clinical studies

The following data were extracted from each clinical study: general information (first author, year of publication, and type of study), clinical characteristics (medications [or drugs] used for ADT, neuropsychological and other tests used in the study, place of patient recruitment, number and grouping of patients, age of patients, age of education, prostate cancer-specific antigen [PSA] levels versus testosterone levels, and duration of follow-up), and conclusions (whether ADT affects cognitive function).

Preclinical studies

The following data were extracted from each preclinical study: general information (first author and year of publication), experimental models and methods (breed, strain, age, sex, and body weight of experimental animals; sample size; method of castration; and method used for cognitive assessment), and conclusions (whether ADT affects cognitive function).

Table 1 Summary of clinical studies on whether ADT affects cognitive function

Author (reference)	Study type	ADT	Study using neuropsychological testing	Recruitment for the study	Number of participants	Age	Education levels (years)	PSA(ng/ml)	testosterone(ng/ml)	Follow-up	Cognitive function related conclusion	Cognitive function declined or not
Salminen, 2003	Prospective study	Flutamide + LHRHa	CogniSpeed software MMSE	/	25ADT 52HC	64.40 ± 6.50 65.30 ± 6.60	8.90 ± 2.90 8.50 ± 2.10	31.00 ± 25.4 /	/ /	Baseline, 6 months, 12 months	ADT is not associated with decline in cognitive function	×
Salminen, 2004	Prospective study	Flutamide + LHRHa	CogniSpeed software MMSE	1999–2002 South-Western Finland	23ADT	65.00 ± 6.70	8.50 ± 3.10	28.00	/	Baseline, 6 months, 12 months	ADT can affect cognitive function in visuomotor slowing, slowed reaction times in some attentional domains	√
Jenkins, 2005	Prospective study	Cyproterone acetate + goserelin	AVLT FAS KCDT NART ROCF WMS-III	/	32ADT 18HC	67.50 ± 4.70 65.40 ± 5.30	/ /	/ /	/ /	Baseline, 3 months, 9 months	ADT can affect cognitive function modestly in short term	√
Beer, 2006	Prospective study	/	MMSE WAIS-R	/	18ADT 17HC	68.90 ± 2.50 63.90 ± 2.00	15.60 ± 0.60 15.70 ± 0.60	/ /	≤5 /	Baseline, 1 month	ADT can affect cognitive function in working memory speed	√

Table 1 (continued)

Author (reference)	Study type	ADT	Study using neuropsychological testing	Recruitment for the study	Number of participants	Age	Education levels (years)	PSA(ng/ml)	testosterone(ng/ml)	Follow-up	Cognitive function related conclusion	Cognitive function declined or not
Cherrier, 2009	Prospective study	Leuprolide + flutamide	PSRLT SCWIT SOPT VKMROT WAIS-R WMS-R	The Genito-urinary clinic at the Seattle Cancer Care Alliance and the Urology clinics at the University of Washington Medical Center (UWMC)	19ADT 19HC	62.05 ± 7.19 65.47 ± 7.99	16.30 ± 3.01 17.38 ± 2.55	/ /	/ /	Baseline, 3 months, 9 months, 12 months	ADT can affect cognitive function	√
Nedelec, 2009	Prospective study	Non-steroidal antiandroge-ns	GBRT MADRS TMT WAIS-III WMS-III	/	14ADT	78.00 ± 4.00	/	1.20 ± 0.64	3.63 ± 1.29	Baseline, 6 months, 12 months	ADT cannot affect cognitive function	×
Alibhai, 2010	Prospective study	/	BVMT CALT COWAT CVLT D-KEFS JLO MMSE NAART SPWM TMT WAIS-III WMS-III	2004.05–2007.09 The Princess Margaret Hospital and the Odette Cancer Centre	77ADT 82PCa patients 82HC	69.30 ± 6.90 69.60 ± 6.70 67.90 ± 7.30	15.25 ± 1.04 16.00 ± 1.24 16.25 ± 1.03	/ / /	/ / /	Baseline, 6 months, 12 months	12 months-ADT is not associated with decline in cognitive function	×

Table 1 (continued)

Author (reference)	Study type	ADT	Study using neuropsychological testing	Recruitment for the study	Number of participants	Age	Education levels (years)	PSA(ng/ml)	testosterone(ng/ml)	Follow-up	Cognitive function related conclusion	Cognitive function declined or not
Mohile, 2010	Prospective study	/	WAIS-III COWAT RFT HVLT-R BVMT-R TMT	The University of Chicago Hospitals	21ADT	71	15	/	/	Baseline, 6 months	ADT can affect cognitive function	√
Chao, 2012	Prospective study	Bicalutamide + goserelin	fMRI the N-back task the stop-signal task	2009.01–2010.12 The Veterans Affairs (VA) Connecticut Healthcare System	15ADT 15HC	69.00 ± 5.30 66.10 ± 6.20	Mainly high school	/ /	0.14 ± 0.10	Baseline, 6 months, 12 months	ADT cannot affect cognitive function, but the impairment of functional brain connectivity can be observed on fMRI	×
Chao, 2013	Prospective study	Bicalutamide + goserelin	fMRI MMSE the N-back task	The Medical Oncology and Urology Clinics at the Veterans Affairs (VA) Connecticut Healthcare System	12ADT 12HC	69.10 ± 5.60 65.50 ± 6.60	Mainly high school and college	/ /	0.16 ± 0.11 2.88 ± 1.01	Baseline, 6 months	ADT causes gray matter volume decreased and decline in cognitive function	√

Table 1 (continued)

Author (reference)	Study type	ADT	Study using neuropsychological testing	Recruitment for the study	Number of participants	Age	Education levels (years)	PSA(ng/ml)	testosterone(ng/ml)	Follow-up	Cognitive function related conclusion	Cognitive function declined or not
Gunlusoy, 2017	Prospective study	/	FAB MoCA	2014.04–2016.02	78ADT 78RP	67.12 ± 5.12 66.84 ± 4.67	/ /	14.12 ± 7.11 6.55 ± 2.03	< 50 /	Baseline, 6 months, 12 months	ADT can affect cognitive function in language ability, short-term memory capacity, mental flexibility and inhibitory control	√
Morote, 2017	Prospective study	LHRHa	WAIS-III 3D-Rotation ad hoc visual memory test JLO	2010.12–2013.02	308ADT	71.20 ± 8.10	/	59.60 ± 386.60	< 20	Baseline, 6 months	6 months-ADT is not associated with decline in cognitive function	×
Ceylan, 2019	Prospective study	/	MoCA	2014.04–2017.02	72ADT 72surgery	67.27 ± 5.06 66.65 ± 4.55	8.00 ± 3.81 6.90 ± 3.05	14.37 ± 3.20 6.57 ± 2.56	< 50 /	Baseline, 6 months, 12 months	ADT can affect cognitive function and increase the risk of depression	√

Table 1 (continued)

Author (reference)	Study type	ADT	Study using neuropsychological testing	Recruitment for the study	Number of participants	Age	Education levels (years)	PSA(ng/ml)	testosterone(ng/ml)	Follow-up	Cognitive function related conclusion	Cognitive function declined or not
Garland, 2021	Prospective surgery	/	ECog	2008.09–2013.10 Florida Institutional Review Board	83ADT	67.92 ± 8.72	Mainly 13–16 years	/	/	Baseline, 6 months, 12 months, 24 months	Patients with ADT are more likely to experience cognitive decline in the presence of insomnia	√
					92PCa patients	67.82 ± 7.46		/	/			
					112HC	68.41 ± 8.26		/	/			
Sánchez-Martínez, 2021	Prospective study	LHRHa	Bcog MMSE	2018.01–2020.03	33ADT	70.80 ± 9.80	Mainly primary studies	1.86 ± 2.50	/	Baseline, 12 months	ADT cannot affect cognitive function	×
Buskbjerg, 2021	Prospective study	LHRHa (leuprolide)	COWAT HVLT-R MRI TMT WAIS-IV WCST WMS-III	2018.02–2019.09 Aarhus University Hospital, Randers Hospital, and Holstebro Hospital	37PCa patients	71.10 ± 5.20	14.10 ± 3.30	16.10 ± 17.22	0.36 ± 0.25	Baseline, 6 months	ADT can affect cognitive function and COMT Met homozygote PCa patients are more at risk	√
					27HC	70.20 ± 7.80	15.40 ± 3.10	/	/			

Table 1 (continued)

Author (reference)	Study type	ADT	Study using neuropsychological testing	Recruitment for the study	Number of participants	Age	Education levels (years)	PSA(ng/ml)	testosterone(ng/ml)	Follow-up	Cognitive function related conclusion	Cognitive function declined or not
Tulk, 2021	Prospective study	/	COWAT FACT-Cog HVLT-R WAIS-IV	The Dr. H. Bliss Murphy Cancer Centre	24ADT	69.63 ± 5.04	Mainly college	< 10	/	Baseline, 12 months	Among the patients who received ADT, men with subjective CRCI are more likely to suffer cognitive impairment, anxiety, fatigue and insomnia	√
Cinar, 2021	Prospective study	Bicalutamide + leuprolide	BVMT- R CVLT-II SDMT TMT	/	48ADT	69.08 ± 4.77	/	8.00 ± 14.00	1.23 ± 0.65	Baseline, 3 months, 6 months	ADT cannot affect cognitive function	×
Myers, 2022	RCT	LHRHa or other forms of androgen blockade	AVLT CTT PROMIS WAIS-IV	/	12ADT 12HC	66.40 71.80	Mainly college or college graduate	/ /	/ /	Baseline, 6 months, 12 months	ADT cannot affect cognitive function	×
Araújo, 2022	Prospective study	Bicalutamide	MoCA	2018.02–2020.03 The Portuguese Institute of Oncology of Porto	366ADT	67.80 ± 7.27	6.33 ± 4.45	/	/	Baseline, 12 months	ADT can affect cognitive function	√

Table 1 (continued)

Author (reference)	Study type	ADT	Study using neuropsychological testing	Recruitment for the study	Number of participants	Age	Education levels (years)	PSA(ng/ml)	testosterone(ng/ml)	Follow-up	Cognitive function related conclusion	Cognitive function declined or not
Chaudhary, 2022	Prospective study	Bicalutamide + goserelin or leuprolide	MoCA MRI the N-back task	The West Haven VA Connecticut Healthcare System	28ADT	66.90 ± 6.90	13.70 ± 3.60	/	/	Baseline, 6 months	6 months-ADT cannot affect cognitive function	×
					38HC	64.50 ± 8.20	14.60 ± 2.90	/	/			

3D-Rotation, mental rotation of three-dimensional objects; *ADT*, androgen deprivation therapy; *AVLT*, auditory-verbal learning test; *BCog*, the brief scale for cognitive evaluation; *BVMT*, Brief Visual Memory Test; *BVMT-R*, the Brief Visual Spatial Learning Test-Revised; *CALT*, Conditional Associative Learning Test; *CTT*, Color Trails Test; *COWAT*, the Controlled Oral Word Association Test; *CRCI*, cancer-related cognitive impairment; *CVLT*, California Verbal Learning Test; *CVLT-II*, the California Verbal Learning Test, second edition; *D-KEFS*, Delis-Kaplan Executive Function System; *ECog*, Everyday Cognition Scale; *FAB*, Frontal Assessment Battery tests; *FAS*, phonemic verbal fluency task; *HC*, healthy control; *GBRT*, Grober-Buschke, Rey Test; *HVLT-R*, the Hopkins Verbal Learning Test-Revised; *JLO*, Judgement of Line Orientation; *KCDT*, Kendrick Assessment of Cognitive Ageing; *LHRHa*, luteinizing hormone releasing hormone analogue; *MADRS*, Montgomery Asberg Depression Rating Scale; *MMSE*, The Mini-Mental Status Examination; *MoCA*, The Montreal Cognitive Assessment; *MRI*, magnetic resonance imaging; *NA*, nonsteroidal antiandrogens; *NAART*, The North American Adult Reading Test; *NART*, the National Adult Reading Test; *PC*, prostate cancer; *PROMIS*, Patient-Reported Outcomes Measurement Information System Applied Cognition–General Concerns and Abilities Short Forms; *PSRLT*, Puget Sound Route Learning Test; *ROCF*, the Rey-Osterrieth Complex Figure; *RP*, radical prostatectomy; *SCWIT*, Stroop Color Word Interference Task; *SDMT*, Symbol Digit Modalities Test; *SOPT*, Subject Ordered Pointing Task; *SPWM*, Spatial Working Memory Task; *The FACT-COG*, the Functional Assessment of Cancer Therapy Cognitive subscale; *TIADL*, Timed Instrumental Activities of Daily Living Test; *TMT*, the Trail Making Test; *VKMROT*, Vandenberg and Kuse Mental Rotation Test; *WAIS-III*, Wechsler Adult Intelligence Scale III; *WAIS-IV*, Wechsler Adult Intelligence Scale IV; *WAIS-R*, Wechsler Adult Intelligence Scale–Revised Vocabulary subtest; *WCST*, Wisconsin Card Sorting Test; *WMS-III*, Wechsler Memory Scale–III; *WMS-R*, Wechsler Memory Scale—Revised

Quality assessment

The quality of the included studies was assessed by three researchers independently (Mengfan Cui, Liming Chen, and Shimin Liu), and any disagreements were resolved by reaching a consensus.

The quality of cohort clinical studies was assessed using the Newcastle–Ottawa Scale (NOS) [20]. In the "Selection" section of NOS, studies that included individuals with localized prostate cancer who had been receiving ADT for at least 6 months were considered true representatives of the exposed cohort and were assigned one point. In the "Selection of the Non-Exposed Cohort" section, studies including patients with localized prostate cancer who did not receive ADT or healthy individuals represented the non-exposed cohort and were assigned one point. In the "Comparability" section, four points were assigned to studies providing information on age, education level, testosterone levels, and other factors. Finally, in the "Outcome" section, one point was assigned to studies that exclusively reported cognitive performance as assessed by cognitive tests. In addition, one point was assigned to studies with a follow-up of at least ≥ 6 months, with a minimum follow-up adequacy of 80%, and one point was assigned to studies with a long-term follow-up with documented data and a description of participants lost. Studies with a minimum NOS score of 6 (out of 9) were considered to be of high quality. The quality of randomized controlled trials (RCTs) was assessed using the modified Cochrane Collaboration risk-of-bias tool (Cochrane Handbook for Systematic Reviews of Interventions version 6.2). Each included study was evaluated for each item in the tool. Studies that completely met the criteria were identified to have a "low risk of bias" and were assigned a score of 1, indicating that the study quality was high. Studies with some missing information were identified to have an "unclear risk of bias" and were assigned a score of 0. Studies that did not meet the criteria at all were identified to have a "high risk of bias" and were assigned a score of 0, indicating that the study quality was low. The quality of preclinical studies was assessed following the Animal Research: Reporting of In Vivo Experiments version 2.0 (ARRIVE 2.0) guidelines [23]. For each animal study, 21 parameters were reviewed in detail, including study design, sample size, inclusion and exclusion criteria, randomization, blinding, outcome measures, statistical methods, experimental animals, experimental procedures, results, abstract, background, objectives, ethical statement, housing and husbandry, animal care and monitoring, interpretation/scientific implications, generalizability/translation, protocol registration, data access, and declaration of interests. If an article clearly provided the aforementioned information, it was marked "reported." If an article provided partial information or lacked the information but did not explain the specific underlying reasons, it was marked "unclear." If an article did not provide the abovementioned information at all or conform to the design recommended by the guidelines, it was marked "not reported." This review has been registered on PROSPERO (CRD42022380347).

Risk of bias

Study quality and risk of bias were assessed by three reviewers independently (Mengfan Cui, Liming Chen, and Shimin Liu), and any disagreements were resolved by reaching a consensus. The risk of bias was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool [24]. The tool consists of ten items with specific signaling questions. For each item, the risk of bias was classified as high, low, or unclear. "Yes" and "No" indicated a high and low risk of bias, respectively, whereas "Unclear" indicated the lack of sufficient information for assessing the risk of bias adequately. If one or more sub-issues were partially met, the risk of bias was unclear; if no sub-issues were met, the risk of bias was high.

Statistical analysis

The data of cognitive function testing reported in the included studies were qualitatively analyzed to assess whether ADT affects cognitive function. If significant differences were observed in at least one or more cognitive function assessment results ($P < 0.05$), ADT was considered to have an effect on cognitive function. We summarized the conclusions of clinical studies and preclinical studies and plotted the percentage loop. The methods for analyzing the studies included in the meta-analysis are provided in the supplementary materials.

Results

Literature search

Clinical studies

A total of 515 potentially eligible articles were preliminarily retrieved via a systematic literature search in the PubMed/Medline, Embase, Web of Science, and Cochrane databases. Of these 515 articles, 244 duplicated articles were excluded. After reading the titles and abstracts, we removed 229 articles. After reading the full text, we removed seven articles owing to the lack of important follow-up data, In addition, we excluded ten articles owing to the lack of experimental data and four articles due to the duplicated study populations from the same recruitment site. Eventually, a total of 21 clinical studies were included [12, 25–44]. There were

few studies using the same neuropsychological test, and only five studies were included in the meta-analysis [25, 26, 31, 33, 41]. The literature screening protocol and results are shown in Fig. 1.

Preclinical studies

A total of 43 potentially eligible articles were preliminarily retrieved via a systematic search in the PubMed/Medline, Embase, Web of Science, and Cochrane databases. Of these 43 articles, 12 duplicated articles were excluded. After reading the titles and abstracts, we removed 16 articles. After reading the full text, we removed two articles owing to the lack of description of cognitive assessment methods and data related to cognitive assessment. Eventually, a total of 13 preclinical studies were included [45–59]. The literature screening protocol and results are shown in Fig. 2.

Study characteristics and qualitative analysis

The 21 clinical studies included a total of 1308 patients with prostate cancer treated with ADT (test group) and 404 healthy individuals, including 211 patients with prostate cancer not receiving any treatment (control group). The 13 preclinical studies included a total of 673 rats and 155 mice (age, 4–12 weeks; body weight: rats, 180–320 g; mice, 18–22 g). For each study, we summarized the age and weight of patients or animals, animal breed or institution of recruitment, form of ADT received, method used to assess cognitive function, conclusions, and effects of ADT on cognitive function. Detailed information regarding the included studies is summarized in Tables 1 and 2.

Quality assessment

Clinical studies

The average NOS score of the 21 clinical studies was 6.76 (higher than 6, out of 9), indicating that the studies were of high quality. The comparability of studies that had a before-and-after design was relatively poor. The details of NOS scoring are provided in Table 3.

Preclinical studies

According to the ARRIVE 2.0 guidelines, the 13 preclinical studies clearly provided information regarding study design, sample size, inclusion and exclusion criteria,

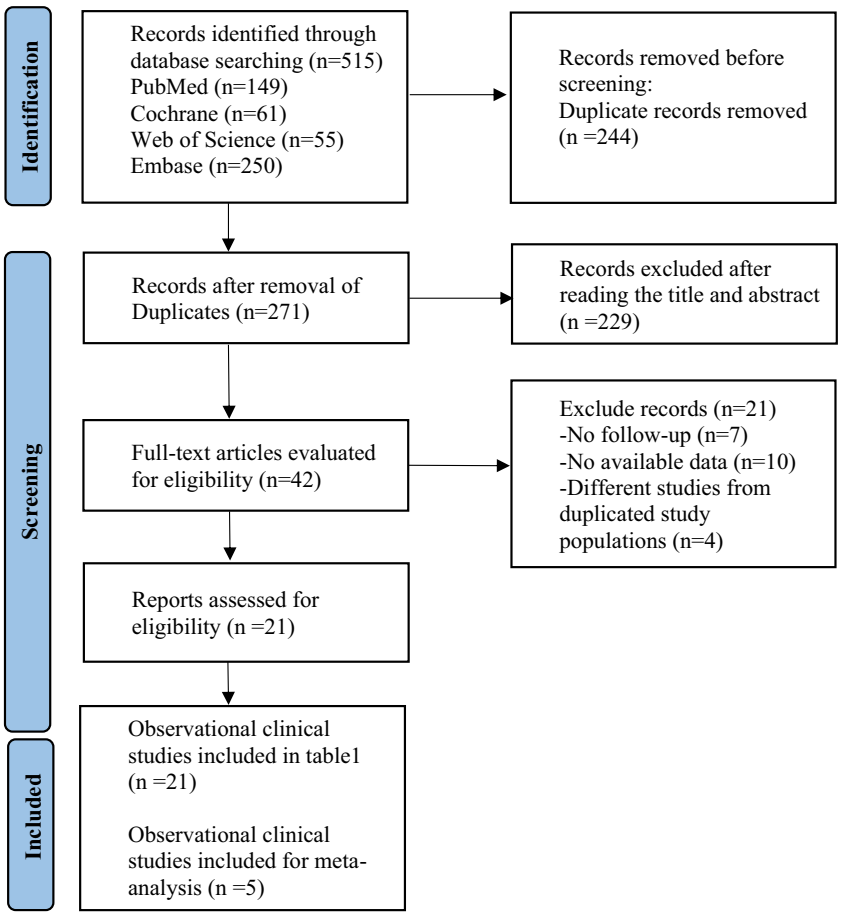

Fig. 1 Flow diagram for study selection process

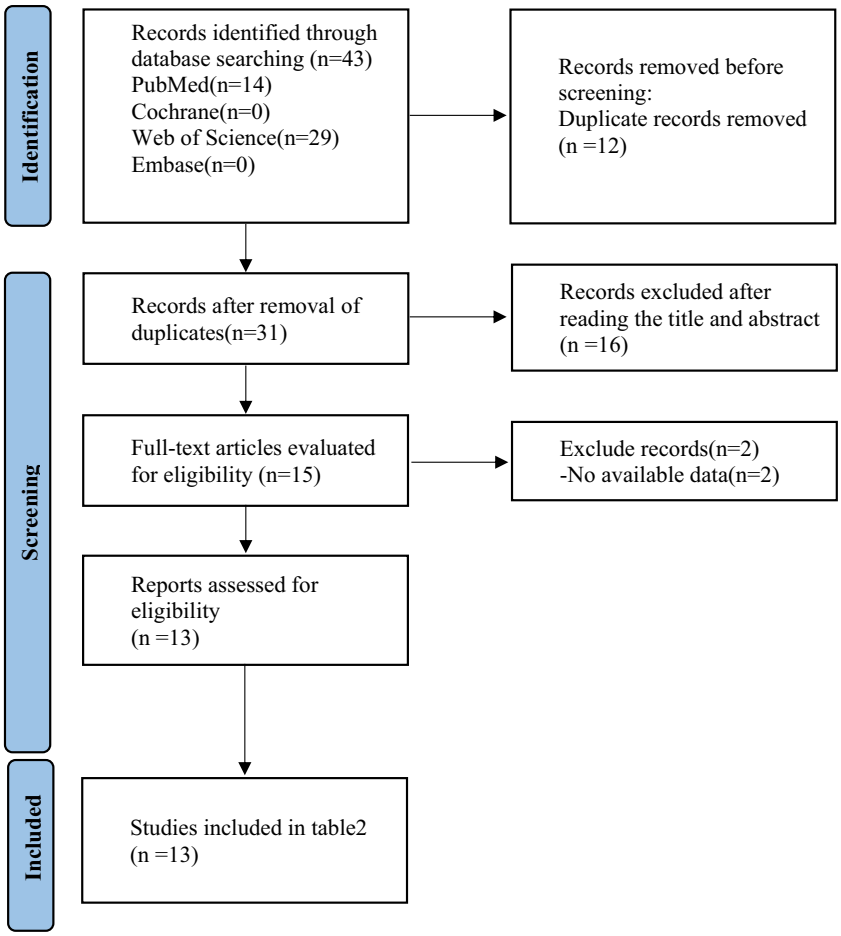

Fig. 2 Flow diagram for study selection process

outcome measures, statistical methods, fexperimental animals, experimental procedures, results, abstract, housing and husbandry, animal care and monitoring, interpretation/scientific implications, and generalizability/translation. However, more significant discrepancies were observed in the reporting of studies with a randomized and blinded design. The details of the scoring are shown in Fig. 3.

Risk of bias

The only RCT among the included clinical studies had a high risk of bias in terms of blinding [43]. All clinical studies lacked allocation concealment and randomization of outcome assessment. According to the results of the SYRCLE tool, none of the preclinical studies had a low risk of bias. All preclinical studies failed to present well in terms of allocation concealment, blinding of participants and investigators, randomization of outcome assessment, and blinding of outcome assessment. The details of the scoring are shown in Table 4.

Cognitive function assessment

Clinical studies

Of the 21 clinical studies, 12 studies concluded that ADT affected cognitive function in patients with prostate cancer [12, 25, 31, 33–40, 44], whereas the remaining nine studies concluded that ADT did not significantly affect or had no effect on cognitive function [26–30, 32, 41–43]. These conclusions are demonstrated in Fig. 4. A neuropsychological test battery was designed to assess eight cognitive-related domains in each study (immediate span of attention, processing speed, verbal fluency, visuospatial ability, verbal learning and memory, visual learning and memory, executive functions of working memory, and executive functions of cognitive flexibility). Neuropsychological tests were the primary component of the test battery. Of the 21 studies, 18 studies reported the use of at least two or more neuropsychological tests for assessing cognitive function in patients with prostate cancer. Collectively, a total of 48 neuropsychological tests and batteries were used for cognitive function assessment. Ten studies chose

Table 2 Summary of preclinical studies on whether ADT affects cognitive function

Author	Year	Animals	Breed	Age	Sex	Weight(g)	Sample number	Castration model	Cognitive and behavioral tests	Conclusion	Cognitive function declined or not
Lagunas	2011	Rats	Wistar	8 weeks	Male	314 ± 6	88	Bilaterally orchidectomized under anesthesia Sham-operated	The cross-maze test	Androgen deprivation can cause cognitive impairment	√
Mcconnell	2012	Rats	SD	4 weeks	Male	/	95	Bilaterally gonadectomy under anesthesia Sham-operated	OLMT	Testicular androgens are important for maximal levels of spatial working memory in male rats	√
Hajali	2015	Rats	SD	10–12 weeks	Male	200–250	96	Bilaterally gonadectomy under anesthesia Sham-operated	MWM	Androgen deprived rats performed worse than health controls in spatial memory	√
Betancourt	2016	Rats	SD	8–12 weeks 8–12 weeks	Male Female	/ /	47 20	Bilaterally gonadectomy under anesthesia Sham-operated	Barnes maze testing OFT	Androgen deprivation can impair cognitive function and executive function in male rats	√
Pintana	2016	Rats	Wistar	5–6 weeks	Male	180–200	72	Bilaterally gonadectomy Under anesthesia Sham-operated	OFT MWM	Androgen deprivation can cause cognitive impairment via impaired hippocampal synaptic plasticity and reduced hippocampal dendritic spine numbers	√
Chunchai	2018	Rats	Wistar	/	Male	180–200	24	Bilaterally gonadectomy under anesthesia Sham-operated	MWM OFT NOLT NORT	Androgen deprivation aggravates cognitive decline in obesity via increasing oxidative stress, glial activity and apoptosis	√
Zhao	2018	Mice	C57BL/6	8 weeks	Male	/	80	Bilaterally orchidectomized under anesthesia Sham-operated	MWM	Androgen deprivation affects cognitive function modestly	×
Ciprés-Flores	2019	Rats	Wistar	10 weeks	Male	200–220	48	Bilaterally orchidectomized under anesthesia Sham-operated	PAT	Androgen deprivation can cause significant cognitive deficits	√

Table 2 (continued)

Author	Year	Animals	Breed	Age	Sex	Weight(g)	Sample number	Castration model	Cognitive and behavioral tests	Conclusion	Cognitive function declined or not
Keawtep	2019	Rats	Wistar	/	Male	180–200	60	Bilaterally orchidectomized under anesthesia Sham-operated	MWM OFT	Androgen deprivation aggravated cognitive impairment in an obese insulin-resistant condition	√
Sharp	2019	Rats	SD	8 weeks	Male	225–250	45	Surgically castrated	AST	Androgen deprivation can cause cognitive impairment	√
Yang	2020	Mice	C57BL/6J	4–6 weeks	Male	18–22	50–75	Bilaterally gonadectomy under anesthesia Sham-operated	MWM OFT PT	Androgen deprivation can cause spatial and learning impairment in mice	√
Muthu	2021	Rats	Wistar	/	Male	250–300	36	Bilaterally orchidectomized under anesthesia Normal control	OFT Elevated plus maze	Androgen deprived rats behaved more anxious and depressive than normal controls	√
Yawson	2021	Rats	Wistar	/	Male	/	42	Bilaterally orchidectomized under anesthesia Normal control	The Y-maze test MWM	Androgen deprivation can cause cognitive impairment	√

AST *attentional* set-shifting test, *EPM* elevated plus maze, *MWM* Morris water maze, *NOLT* novel object location test, *NORT* novel object recognition test, *OFT* the open-field test, *OLMT* object location memory test, *PAT*, the passive avoidance training test, *PT* pole test, *SD* Sprague–Dawley

Table 3 NOS scores

Selection			Comparability				Outcome			
Included studies	Representativeness of the exposed cohort/sample	Ascertainment of exposure	On age	On education	On testosterone	On other factors	Assessment of outcome	Long-enough follow-up	Completeness of follow-up of cohorts	Score
Salminen, 2003	*	*	*	*	-	*	*	*	*	8/9*
Salminen, 2004	*	-	*	*	-	*	*	*	*	7/9*
Jenkins, 2005	*	*	*	-	-	-	*	*	*	6/9*
Beer, 2006	*	-	*	*	*	-	*	-	*	6/9*
Cherrier, 2009	*	*	*	*	-	-	*	*	*	7/9*
Nedelec, 2009	*	-	*	-	*	*	*	*	*	7/9*
Alibhai, 2010	*	*	*	*	-	-	*	*	*	7/9*
Mohile, 2010	*	-	*	-	-	*	*	*	*	6/9
Chao, 2012	*	*	*	*	*	-	*	*	*	8/9*
Chao, 2013	*	*	*	*	*	-	*	*	*	8/9*
Gunlusoy, 2017	*	-	*	-	*	*	*	*	*	7/9*
Morote, 2017	*	-	*	-	*	*	*	*	*	7/9*
Ceylan, 2019	*	-	*	*	*	*	*	*	*	8/9*
Garland, 2021	*	*	*	*	-	-	*	*	*	7/9*
Sánchez-Martínez, 2021	*	-	*	*	-	*	*	*	*	7/9*
Buskbjerg, 2021	*	*	*	*	*	*	*	*	*	9/9*
Tulk, 2021	*	-	*	*	-	*	*	*	*	7/9*
Cinar, 2021	*	-	*	-	*	*	*	*	*	7/9*
Araújo, 2022	*	-	*	*	-	-	*	*	*	6/9*
Chaudhary, 2022	*	*	*	*	-	-	*	*	*	7/9*

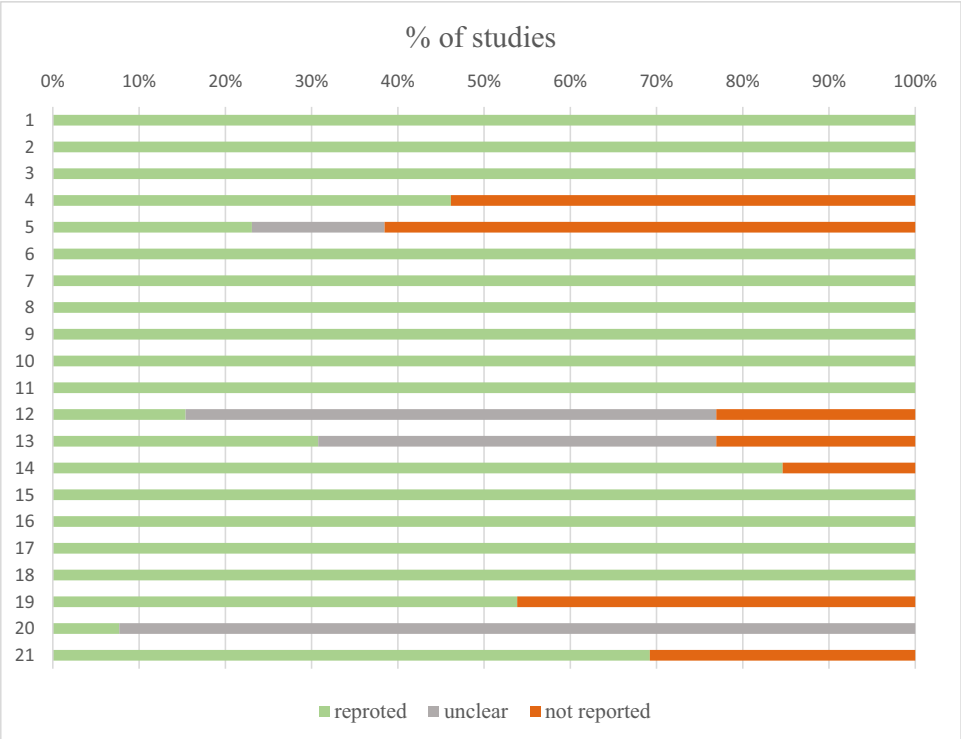

Fig. 3 1: study design; 2: sample size; 3: inclusion and exclusion; 4: randomization; 5: blinding; 6: outcome measures; 7: statistical methods; 8: experimental animals; 9: experimental procedures; 10: results; 11: abstract; 12: background; 13: objectives; 14: ethical statement; 15: housing and husbandry; 16: animal care and monitoring; 17: interpretation/scientific implication; 18: generalizability/translation; 19: protocol registration; 20: data access; 21: declaration of interests

Table 4 The SYRCLE scores of preclinical studies

Included studies	SYRCLE items									
	1	2	3	4	5	6	7	8	9	10
Lagunas, 2011	n	y	n	n	n	n	n	y	y	y
Mcconnell, 2012	n	n	n	n	n	n	y	y	y	y
Hajali, 2015	n	n	n	n	n	n	y	y	y	y
Betancourt, 2016	n	n	n	n	y	n	n	y	y	y
Pintana, 2016	n	n	n	n	n	n	y	y	y	y
Chunchai, 2018	y	y	n	n	n	n	n	y	y	y
Zhao, 2018	y	y	n	y	n	n	n	y	y	y
Ciprés-Flores, 2019	y	y	n	y	n	n	y	y	y	y
Keawtep, 2019	n	n	n	n	n	n	n	y	y	y
Sharp, 2019	n	n	n	n	n	n	n	y	y	y
Yang, 2020	y	y	n	y	y	n	n	y	y	y
Muthu, 2021	y	n	n	y	n	n	n	y	y	y
Yawson, 2021	n	n	n	n	n	n	n	y	y	y

1, sequence generation; 2, baseline characteristics; 3, allocation concealment; 4, random housing; 5, blinding of participants and personnel; 6, random outcome assessment; 7, blinding of outcome assessment; 8, incomplete outcome data; 9, selective outcome reporting; 10, other bias; y, low risk of bias; ?, unclear; n, high risk of bias

the Wechsler Adult Intelligence Scale or the Wechsler Memory Scale, covering multiple cognitive functions, as one of the main compositions in the cognitive function assessment. Among The five studies included in the meta-analysis, we found that only two neuropsychological tests, the Mini-Mental Status Examination (MMSE) and Digit Span, were suitable for completing the data analysis. The forest plot of MMSE shows that ADT use has a significant effect on cognitive decline, the same conclusion was not evident in the Digit Span test. The detailed statistical methods and results of the forest map are shown in the supplementary data Fig. 1 and Fig. 2.

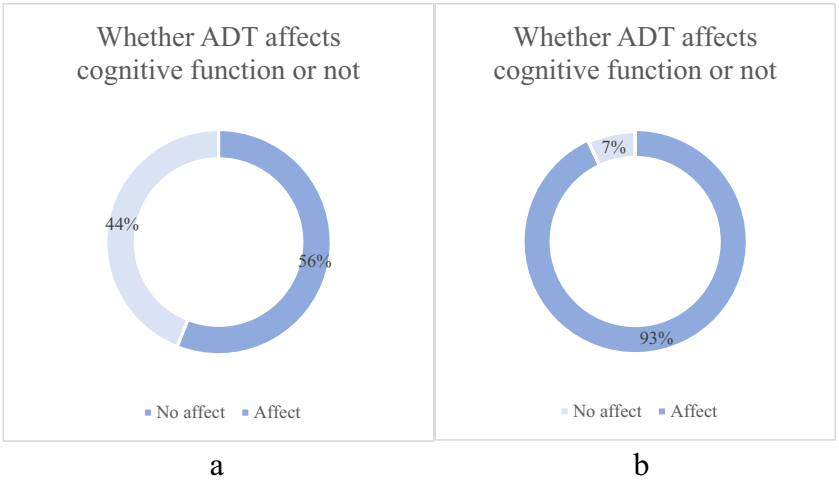

Fig. 4 (**a**) Whether ADT affects cognitive function or not in clinical studies (**b**) Whether ADT affects cognitive function or not in preclinical studies

Preclinical studies

Of the 13 included studies, 12 studies concluded that bilateral orchiectomy caused cognitive decline in rats or mice, whereas only one study concluded that castration did not cause significant cognitive impairment in young mice. These conclusions are demonstrated in Fig. 4. All included studies used behavioral tests to assess cognitive function in rats or mice. A total of seven studies reported the use of the Morris water maze (MWM) test. In addition, other similar maze tests, including the Barnes maze test, cross-maze test, and Y-maze test, were used. MWM was most frequently used in the included preclinical studies, indicating that the test is highly recognized for the assessment of cognitive function in rats or mice.

Discussion

Effects of ADT on cognitive function

Androgens are required for the growth of prostate cancer cells [4]. ADT inhibits the development of prostate cancer by suppressing androgens. Androgens are classified as C-19 steroids and are mainly secreted by the testes and adrenal cortex [60]. Testosterone (T) and its 5α-reduced derivative 5a-dihydrotestosterone (DHT) are the most prevalent androgens in the human body [61]. Androgens play an important role in cognitive function. They can readily cross the blood–brain barrier and control the central nervous system (CNS) [62]. Androgen receptors are widely distributed in the brain. Westlye et al. [63] reported that androgen receptors are highly expressed in the amygdala, brainstem, hypothalamus, and cerebral cortex. These regions play a dominant role in cognitive function and emotion regulation [64]. However, the expression of androgen receptors is decreased when the parietal cortex and hippocampus are damaged [62]. As an androgen, testosterone prevents tau hyperphosphorylation and regulates the accumulation of β-amyloid, preventing cognitive decline [65]. However, individuals with low testosterone levels are more susceptible to Alzheimer's disease and dementia [66, 67]. The enzyme aromatase uses testosterone to make 17β-estradiol (E2) [68]. The hippocampus, prefrontal cortex, and amygdala, which exert protective effects on cognitive function, are memory-related regions associated with E2 [69]. Therefore, theoretically, the ADT-induced decrease in androgen levels, including testosterone and dihydrotestosterone levels, influences cognitive function [48, 56].

Risk of cognitive decline associated with ADT use

Behavioral tests in preclinical studies have shown impairments in cognitive function, such as spatial learning and working memory, in male mice or rats treated with ADT [46, 51, 52]. Similarly, impairments in visuospatial learning and memory have been observed in patients with prostate cancer treated with ADT [40]. Although ADT has not been proven to affect cognitive function in clinical settings, the risk of cognitive decline cannot be overlooked. Therefore, the ADT-induced decrease in testosterone levels potentially increases the risk of cognitive decline in patients with prostate cancer [36, 67, 70]. Patients should be informed of this risk before the use of ADT.

Limitations of clinical studies on ADT

Differences between study participants were prevalent

Although all of the 21 included clinical studies reported on the effects of ADT on cognitive function in patients with prostate cancer, significant differences were observed in

the baseline characteristics of patients among the studies. First, the age of patients largely varied across studies, ranging from 60 to 80 years. Regarding age at education, some studies did not consider PSA and serum testosterone levels, which are indicators of cognitive function and prostate cancer, at the time of collection of baseline information. Moreover, heterogeneity was high for some indicators, such as PSA levels. A study by Morote et al. reported the highest PSA level of > 400 ng/mL in patients with prostate cancer, which is higher than the average level reported in other studies [28]. PSA is secreted by prostate acinar and ductal epithelial cells, and its production also requires the direct participation of testosterone, so there is a strong correlation between them. To some extent, PSA levels can be used as a proxy for looking at testosterone levels [71]. Popiołek et al. found a strong correlation between PSA levels and verbal memory and executive function test results, and PSA levels and free testosterone levels can be used together as biomarkers to observe cognitive function [72]. Therefore, owing to large differences in baseline characteristics, the prevalent differences among the study population cannot be overlooked. Some inconsistencies in the findings of the included studies may be attributed to the variability of the study population.

Differences among research methodologies

At present, maze-related and neuropsychological tests are the primary methods used to assess cognitive function in preclinical and clinical studies, respectively. The maze-related tests mainly include the MWM test, Barnes maze test, elevated plus maze test, and Y-maze test [73–75]. Of these tests, the MWM test has been most frequently used in preclinical studies and yields comprehensive results. The MWM test reflects the spatial memory and learning ability of animals (rats or mice) by training them and recording the time required by animals to locate a transparent platform in a pool of water [76, 77]. It was first developed by neuroscientist Richard G. Morris in 1981 [78]. Except for maze-related tests, other tests for assessing cognitive function in mice or rats are not yet available.

Neuropsychological tests are most commonly used for assessing cognitive function in clinical studies [79, 80]. These tests reflect the cognitive status and function of patients in a comprehensive manner. Most importantly, these diagnostic tests are non-traumatic for patients. Cognitive functioning comprises seven domains, namely, attention/working memory, executive functioning, language, verbal memory, visual memory, visuospatial ability, and visuomotor ability [81]. Researchers should assess various cognitive domains to obtain a more comprehensive overview of cognitive functioning. Therefore, the protocol of cognitive function assessment varies across studies. Overall, the inconsistency between the findings of clinical and preclinical studies is attributed to two reasons. On the one hand, it is because of the large differences between the two types of study designs, behavioral tests, and neuropsychological tests. On the other hand, it is because there are many factors that should be considered in the design of clinical studies. Therefore, the research design of clinical studies cannot be relatively homogeneous as in the case of preclinical studies.

Table 5 Suggestions for clinical studies on whether ADT affects cognitive function or not

1. There is a clear assessment of indicators related to cognitive functioning in prostate cancer patients. Examples include age, age at education, serum testosterone levels, and other indicators.
2. Addition of other measures of cognitive functioning, e.g., nuclear magnetic resonance, serologic index tests.
3. Use with caution in patients with mild cognitive decline, dementia, Alzheimer's disease, and other cognitive impairments.
4. In studies that focus on cognitive functioning, add the necessary follow-up to track the status of cognitive functioning in a timely manner.

Limitations of neuropsychological testing

With the continual advancement of neuropsychological testing procedures and items, there is a wide variety of versions of neuropsychological tests available. For researchers, it is essential to carefully select the appropriate version of the test. Inappropriate versions will undoubtedly increase researchers' statistical error [82]. In addition, neuropsychological tests require researchers to score the completion performance of participants. This scoring process may lead to information bias. For example, researchers may assign inappropriate subtest and index scores in WAIS or make errors in converting and scaling the scores, eventually leading to inaccurate results [83].

With the advent of the information age and the deepening of neurological research, changes in cognitive function can no longer be understood through neuropsychological testing alone. Chao et al. found that patients with prostate cancer treated with ADT exhibited a significant decrease in frontal lobe activity in the brain and the volume of gray matter on MRI scans. These changes were not readily observable through the neuropsychological tests designed by the authors [31, 32]. MRI and the establishment of brain networks [84], as well as the detection of specific markers related to cognitive aging, such as β-amyloid and APOE4 [85, 86], may facilitate the prevention of cognitive decline.

Conclusions

To the best of our knowledge, this review is the first to summarize and compare the findings of preclinical and clinical studies investigating the effects of ADT on cognitive function. We analyzed the challenges encountered in clinical studies and identified the reasons for inconsistencies in conclusions. Based on the findings of preclinical studies, ADT influences cognitive function. In this review, we first highlighted the importance of consistency in the baseline information of patients in clinical studies. Second, we suggested other measures of cognitive function to facilitate diagnosis and increase the credibility of evidence. Third, we provided recommendations for the use of ADT in patients with prostate cancer whose cognitive function is already declining or those who are at risk of cognitive decline. In addition, we summarized the assessment protocols and prevention guidelines that should be followed before using ADT. Fourth, for patients with cognitive decline, necessary follow-ups should be conducted to achieve long-term monitoring of cognitive function and prompt adjustment of the treatment plan. All of the abovementioned recommendations are mentioned in Table 5. Although ADT is effective in prolonging the survival of patients with prostate cancer, we should pay attention to not only the advantages of ADT but also its side effects. In conclusion, ADT is a double-edged sword, and its use relies on clinical decision-making.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00520-024-08753-3.

Acknowledgements The authors thank Prof. Shimin Liu and Dr. Liming Chen for their contribution to the writing of this manuscript and Prof. Fuwen Yuan and Dr. Danli Jiao for their valuable suggestions regarding the "Discussion" section. The authors also thank all study participants for their contribution and KetengEdit (www.ketengedit.com) for English language editing services.

Author contribution Mengfan Cui, Liming Chen, and Shimin Liu: Designed the research, sought project funding, and searched and analyzed data. Mengfan Cui and Liming Chen: Prepared the manuscript. Mengfan Cui, Liming Chen, Fu-wen Yuan, Chen Zhao, Bing-zhe Ma, and Cindy Jiang: Edited the manuscript. Mengfan Cui and Liming Chen: Conducted the research and composed the final content of the manuscript. All authors have read and approved the final version of this manuscript.

Funding This research was supported by the Scientific Research Project of the Shanghai Municipal Health Commission (No. 202140348).

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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