



Risk of Depression after 5 Alpha Reductase Inhibitor Medication: Meta-Analysis

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Purpose: Although five-alpha reductase inhibitor (5-ARI) is one of standard treatment for benign prostatic hyperplasia (BPH) or alopecia, potential complications after 5-ARI have been issues recently. This study aimed to investigate the risk of depression after taking 5-ARI and to quantify the risk using meta-analysis.

Materials and Methods: A total of 209,940 patients including 207,798 in 5-ARI treatment groups and 110,118 in control groups from five studies were included for final analysis. Inclusion criteria for final analysis includes clinical outcomes regarding depression risk in BPH or alopecia patients. Overall hazard ratio (HR) and odds ratio (OR) for depression were analyzed. Moderator analysis and sensitivity analysis were performed to determine whether HR or OR could be affected by any variables, including number of patients, age, study type, and control type.

Results: The pooled overall HRs for the 5-ARI medication was 1.23 (95% confidence interval [CI], 0.99–1.54) in a random effects model. The pooled overall ORs for the 5-ARI medication was 1.19 (95% CI, 0.95–1.49) in random effects model. The sub-group analysis showed that non-cohort studies had higher values of HR and OR than cohort studies. Moderator analysis using meta-regression showed that there were no variables that affect the significant difference in HR and OR outcomes. However, in sensitivity analysis, HR was significantly increased by age ($p=0.040$).

Conclusions: Overall risk of depression after 5-ARI was significantly not high, however its clinical importance needs validation by further studies. These quantitative results could provide useful information for both clinicians and patients.

Keywords: Alopecia; Depression; Prostatic hyperplasia; Suicide; 5-alpha reductase inhibitors

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INTRODUCTION

Five-alpha reductase inhibitor (5-ARI) is one of the standard treatments for benign prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS), together with alpha blockers for BPH [1,2]. Considering the re-

cent and increasing shift toward medication instead of surgical therapy [3], the clinical efficacy of 5-ARI is in reducing both complications related to BPH/LUTS and the need to perform surgery [4,5]. Five-ARI is also standard treatment in androgenic alopecia, especially for male pattern hair loss (MPHL) because androgen is

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the most common cause of hair loss [6].

Five-ARI blocks the conversion of testosterone to dihydrotestosterone, which accounts for the efficacy of its use in the treatment of BPH/LUTS and MPHL, by reducing prostate volume or promoting regeneration of hair follicles [6,7]. To date, there are two types of 5-ARIs, including finasteride and dutasteride. While finasteride inhibits only type 2 5-alpha reductase (5-AR), dutasteride inhibits both type 1 and 2 5-AR, but both medications have equal efficacy [8].

There have been controversy about long term safety of 5-ARI due to limited evidence has been introduced to date. Due to the potent androgenic activity of dihydrotestosterone, adverse events related to 5-ARI have been reported for 20 years, especially sexual adverse events [9-11]. Moreover, recently, depressive symptoms and suicidal thoughts were more prevalent among the formal users of finasteride who experienced persistent sexual adverse events than the controls [9].

Although there is a controversy, a considerable number of men have reported intolerable adverse effects after initiating finasteride therapy, and they continue to experience these effects after stopping the medication [9,10]. These peripheral or secondary effects have undesirable consequences that are collectively becoming known as post-finasteride syndrome [11]. Currently, US Food and Drug Administration and Health Canada have warned about this crucial issue of adverse events using finasteride during their use for BPH/LUTS and alopecia [12,13].

However, there is only limited academic evidence of adverse events related to taking 5-ARI, including depression and suicidal thoughts or suicide attempts, and those evaluating the evidence are drawing conflicting conclusions [14-16]. Although two prior clinical studies (which are secondary analyses of a previous clinical trial and cohort study) showed the association between depression risk and 5-ARI medication [14,15], recent large case control studies have shown limited association between the use of 5-ARI medication and depression or the risk of suicide attempts [16].

Considering the social burden of depression and suicide attempts, together with that of BPH/LUTS or alopecia [17], more evidence is needed in order to develop better information for both clinicians and patients, which could have benefits regarding shared decision making about 5-ARI use. Our goal of this study is to suggest quantitative information about the risk of de-

pression and suicide attempts after 5-ARI use through the use of systematic review and meta-analysis from current observational studies.

MATERIALS AND METHODS

1. Ethics statement

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [18]. This is a literature-based study, ethical approval is unnecessary.

2. Data sources and literature searches

The electronic databases screened were MEDLINE (1966 through January 2017) and Cochrane Library (1993 through January 2017). Medical subject headings terms were used. The subject headings and text keywords included interventions (5-alpha Reductase Inhibitors; azasteroids, finasteride, and/or dutasteride) and outcomes (depression disorder, suicide and/or suicide thinking). The searches were limited to human studies and performed for all languages & all study types. The same reference searching was adopted for the EMBASE using Emtree (Embase subject headings).

3. Study selection

Study inclusion criteria were as follows: 1) interventions included administration of 5-ARI, 2) participants were diagnosed with depression disorder, suicide and/or suicidal thinking. Two of us (JHK and SRS) independently screened the titles and abstracts of all articles using predefined inclusion criteria. The full-text articles were examined independently by two of authors (JHK and BIC) to determine whether or not they met the inclusion criteria. Then, two of authors (JHK and BIC) independently extracted data using a data extraction form. Final inclusion articles were determined by the all investigators' evaluation discussions, using a point estimation system for each article. References and data for each included study were carefully cross-checked to ensure that no overlapping data were present and to maintain the integrity of the meta-analysis.

4. Types of interventions and outcomes

The experimental group received 5-ARIs and the control group received non-exposure of 5-ARI, placebo, or adrenergic alpha-antagonist. Outcomes measured

hazard ratio (HR) and odds ratio (OR).

5. Types of moderators

In order to identify the moderator effect, continuous variables (age and number of patients) and binary variables (study type: cohort/non-cohort; control type: adrenergic alpha-antagonist/non-expose of 5-ARI) were analyzed.

6. Meta-analysis assessment of outcome findings and statistical analysis

Included studies are those of large populations and long periods – at least one year. These kinds of time-to-event outcomes are most appropriately analyzed using HR. For the absence of individual patient data or HR, Tierney et al [19] well described the practical methods for incorporating summary time-to-event data into meta-analysis. The HRs of three studies [9,14,20] were calculated using Tierney's practical guide [19].

For overall effect size of OR, two studies [9,15] did not report ORs. We calculated ORs using crude depression events. In order to gain deep understanding, we displayed two types of statistical models as the fixed-effects model and the random-effects model. Meta-regression analysis was conducted for each moderator. To examine potential moderators (*e.g.*, number of patients, age, study type, and control type), we used a restricted maximum likelihood estimator of the variance of the true effects.

Sensitivity analysis was conducted for robust interpretation. Due to the fact that one study [9] has relatively small sample sizes and different indication for medication, we excluded that study [9] in sensitivity analysis.

A two-sided p-value ≤ 0.05 or not contained of null value (HR=1 or OR=1) within the 95% was considered to be significant. The abovementioned analyses were conducted with STATA ver. 14.2 software (Stata Corp. LP, College Station, TX, USA).

7. Quality assessment

Newcastle–Ottawa quality scale was used to evaluate for the quality assessment for the case-control and cohort study. We assessed the following three parameters: (1) appropriate selection, (2) comparability of research design or statistical analysis, (3) outcome/exposure ascertainment and research procedure. We graded each parameter as a star; a study can be awarded a

maximum of one star for each item in selection and outcome/exposure, but a maximum of two stars can be awarded in comparability. The quality power of the evidence related to the estimation of benefits and disadvantages were displayed according to specific conditions.

8. Assessment of heterogeneity

Statistical heterogeneity was evaluated by the Cochran's Q test and the I^2 statistic. Either a Cochran's Q statistic $p < 0.1$ or an I^2 statistic $> 50\%$ indicated the existence of significant heterogeneity between studies. However, a non-significant χ^2 test result ($p \geq 0.1$) or I^2 statistic ($\leq 50\%$) indicated a lack of evidence for heterogeneity, but it did not necessarily imply homogeneity because there may have been insufficient statistical power to detect heterogeneity. So, we used two types of statistical models (fixed-effects and random-effects model).

9. Assessment of potential publication bias

We performed comprehensive meta-analysis to examine any potential publication bias in the studies, and the results were shown by funnel plot. In the absence of publication bias, the studies will be distributed symmetrically by the combined effect size. The Begg and Mazumdar rank correlation test and the Egger linear regression test were performed for publication biases.

RESULTS

1. Study selection

The initial search identified a total of 478 articles from electronic databases (PubMed, 62; Cochrane, 10; Embase, 406). Thirty studies were excluded because they contained overlapping data or appeared in more than one database. Upon more detailed review, an additional 417 papers were excluded for the following reasons: unrelated topic ($n=286$), 5-ARI with other topics ($n=45$), other drugs and suicide ($n=4$), *in vitro* experiment ($n=26$), review paper or editorials ($n=56$). After screening the titles and abstracts, 31 studies were determined to be eligible for intensive screening. Of these, 26 studies were further eliminated as they were duplicated supplements and had insufficient outcome data. Finally, five studies met our selection criteria and were included in the meta-analysis (Fig. 1).

A systematic review of the five studies was con-

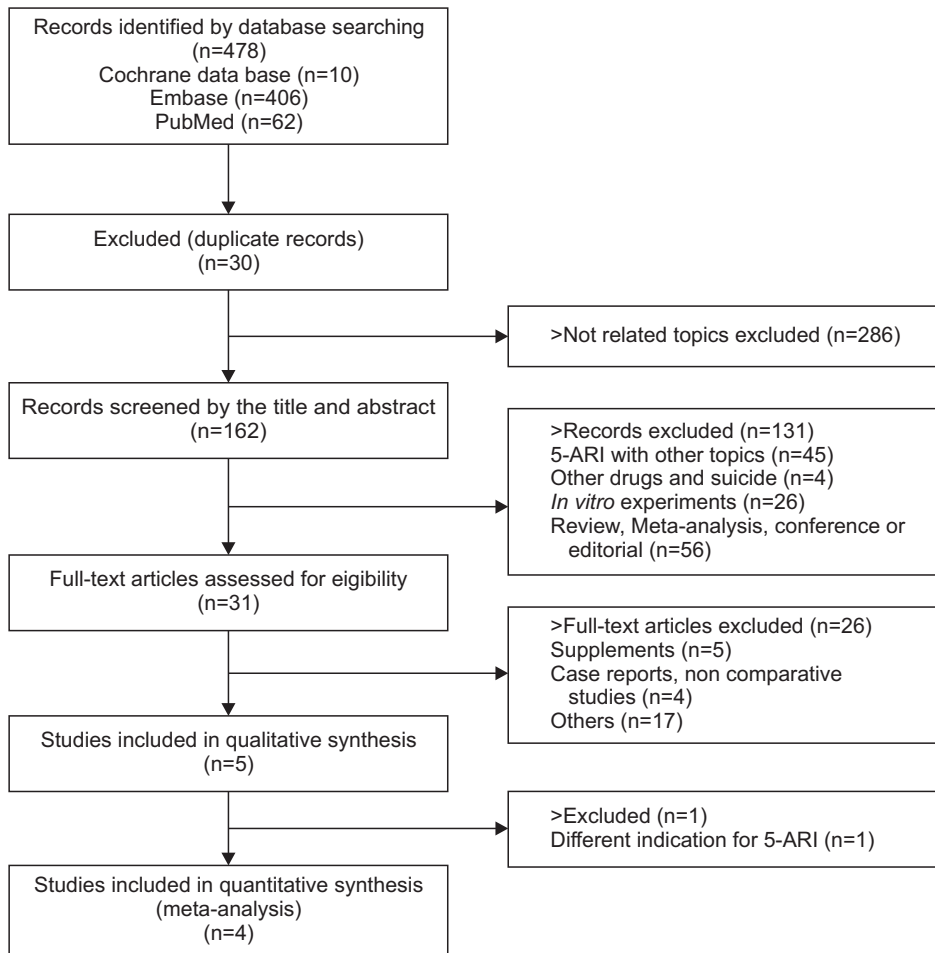


Fig. 1. Flow chart for study inclusion.

ducted to assess detailed experimental differences and subject descriptions for qualitative analysis (Table 1). However, for quantitative analysis only four studies were finally included. Three were cohort studies with large population comparative studies that included a total of 207,798 subjects (99,627 treatment and 108,171 control subjects), and one observational cross-section study that included a total of 2,052 subjects (134 treatment and 1,918 control subjects).

2. Quality assessment

Authors critically appraised the selected studies using criteria given by Newcastle–Ottawa quality scale, and then final quality evaluation was discussed among all investigators (Table 2). All three cohort studies were ranked good quality, and one retrospective case-control study [9] was ranked poor quality due to its relatively small sample size and the fact that its bias control was not adjusted for research analysis.

3. Outcome findings

The pooled overall HRs for the 5-ARI medication was 1.23 (95% confidence interval [CI], 0.99–1.54) in random effects model. The Cochran’s Q test p-value and the I² statistic were p<0.001 and 94%. In subgroup analysis of study types, the pooled overall HRs of the cohort studies were 1.16 (95% CI, 0.92–1.47) in random effects model than the cohort studies (Fig. 2).

The pooled overall ORs for the 5-ARI *versus* the control group were 1.19 (95% CI, 0.95–1.49) in the random effects model. The Cochran’s Q test p-value and the I² statistic were p<0.001 and 94%. In subgroup analysis of study types, the pooled overall ORs of cohort studies were 1.12 (95% CI, 0.86–1.46) in the random effects model (Fig. 3).

Table 3 provided an overview of meta-regression analysis results to identify the moderator effects. The regression analysis with all continuous variables (*e.g.*, number of patients, age, study type, and control type) did not show a significant difference in HR and OR

Table 1. Characteristics of included trials

Study	Country	Study design	Subject for analysis treatment (n)	Subject for analysis control (n)	Medication duration	Subject description	Indication for medication	Assessment for depression
Irwig (2012) [9]	USA	Case-control, retrospective study	Finasteride (61)	Control (29)	<1 year (51%), ≥1 year (49%)	Mean age 31.7 years (finasteride) and 26.2 years (control). Finasteride group was taking the medication for at least 3 months and control group was never used finasteride.	Male pattern hair loss	Beck Depression Inventory-II
Pietrzyk et al (2015) [14]	Poland	Observation, cross section study	5-ARI only (134)	AB only (1,918)	<1 year (21.4%), ≥1 year (78.6%)	Mean age 65.8 years. 4,035 men diagnosed with BPH, control group was never used 5-ARI.	BPH	Beck Depression Inventory
Unger et al (2016) [15]	USA	Cohort study (prospective study)	Finasteride (6,941)	Placebo (6,994)	At least 7 years	Mean age 63.5 years (finasteride) and 63.6 years (placebo). A total of 18,880 patients from PCPT were randomly assigned to finasteride and placebo for 7 years. And then PCPT was linked to Medicare claims 13,395 patients.	To identify the relationship between finasteride and prostate cancer	ICD-9 diagnostic codes
Welk et al (2017) [16]	Canada	Cohort study (retrospective, propensity score matching study)	5-ARI (89,844)	Control (89,844)	1.57–1.60 years	Mean age 75 years. It used 7 types of administrative data sources at Ontario province in Canada. And then it matched with a 5-ARI prescription to those without any 5-ARI prescriptions. Control group is unexposed of 5-ARI.	To identify the relationship between 5-ARI and depression	ICD-9 & 10 diagnostic codes
Hagberg et al (2017) [20]	UK	Cohort study (matching for nested case-control study)	5-ARI only (2,842)	AB only (11,333)	7.6 (5-ARI only) & 7.7 (AB only) person-years/per 1,000 person-years	A 78.4% of total patients are more than 60 years old who identified 77,732 men with benign prostatic hyperplasia. It was conducted using the UK's Clinical Practice Research Datalink.	BPH	Depression diagnostic code and who received a prescription for an antidepressant

5-ARI: alpha reductase inhibitor, AB: adrenergic alpha-antagonist, BPH: benign prostatic hyperplasia, PCPT: Prostate Cancer Prevention Trial, ICD: International Classification of Diseases.

Table 2. Newcastle-Ottawa quality assessment form for case-control study and cohort study

Variable	Selection		Comparability		Outcome/Exposure		Total score	Quality power
For case-control study	Adequate definition of case	Representativeness of case	Selection of control	Definition of control	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non response rate
Irwig (2012) [9]	★	★	★	★	★	★	★	★
Pietrzyk et al (2015) [14]	★	★	★	★	★★	★	★	★
For cohort study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts on the basis of the design or analysis	Ascertainment of outcome	Adequacy of duration of follow-up	Adequacy of completeness of follow-up
Unger et al (2016) [15]	★	★	★	★	★★	★	★	★
Welk et al (2017) [16]	★	★	★	★	★★	★	★	★
Hagberg et al (2017) [20]	★	★	★	★	★★	★	★	★

A study can be awarded a maximum of one star for each numbered item except for Comparability. A maximum of two stars can be awarded for Comparability. Good quality, 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Fair quality, 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Poor quality, 0 or 1 star in selection domain OR 0 or 1 stars in comparability domain AND 0 or 1 stars in outcome/exposure domain.

outcomes. However meta-regression analysis showed that HR was significantly increased by age in cases of inclusion of Irwig et al [9] (Fig. 4). In sensitivity analysis (Supplement 1, 2), both HR and OR was affected by the results of Irwig et al [9].

4. Publication bias

The statistical approaches for the detection of publication bias or small-study effect is shown in Supplement 3. Both funnel plots of HR and OR seemed to be asymmetry graphs because of one skewed study: Irwig et al [9]. In the analysis by HR, however, Begg and Mazumdar's correlation was -0.24 (p=1.000), Egger's regression coefficient was 2.907 (p=0.510), suggesting that there was no evidence of publication bias or small-study effect in this meta-analysis. We also did an analysis of OR, by which we found that there is no significant evidence of publication bias in this meta-analysis.

DISCUSSION

Despite its characterization on the internet as a hot focused social issue due to "life-altering" and "devastating" effects, academic evidence on the use of 5-ARI, especially, finasteride, is not sufficient to show the crucial adverse effects of using 5-ARI medication. Interestingly, a relatively high rate of discontinuation of 5-ARI has been reported compared to other urologic medication [21]. Several patients have a fear of the persistent adverse events which have been publicized on the internet despite evidence to the contrary, which has proven the efficacy of 5-ARI in treating BPH/LUTS and alopecia.

Unfortunately, there is only limited evidence about this issue. Moreover, those studies are not intention to treat trial designs to investigate the risk of depression or suicide. Although designing an randomized controlled trial (RCT) regarding this crucial issue is almost impossible, several limitations of observational studies about drug-related adverse events have to be clarified for better understanding of each study. In addition to the fact that our study has a primary goal to suggest a quantitative risk of depression using meta-analysis, it could clarify the characteristics of each of the observational studies that were included during systematic review. This enables us to give critical information for designing future prospective trials.

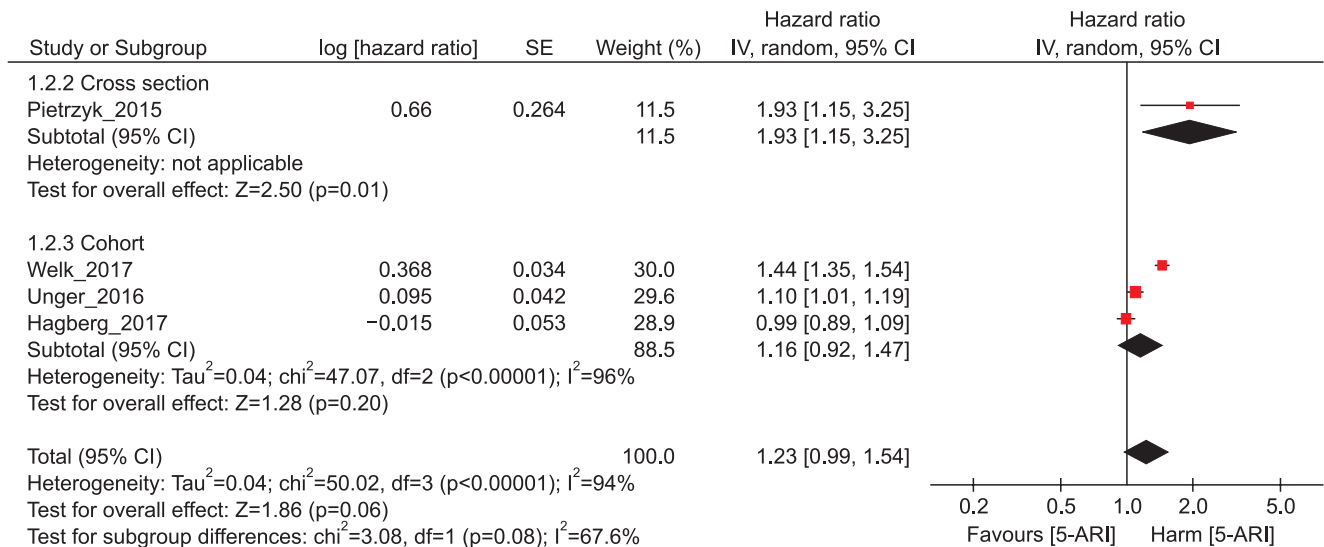


Fig. 2. Hazard ratio of depression among men exposed to five-alpha reductase inhibitor (5-ARI) medication. SE: standard error, CI: confidence interval, df: degree of freedom.

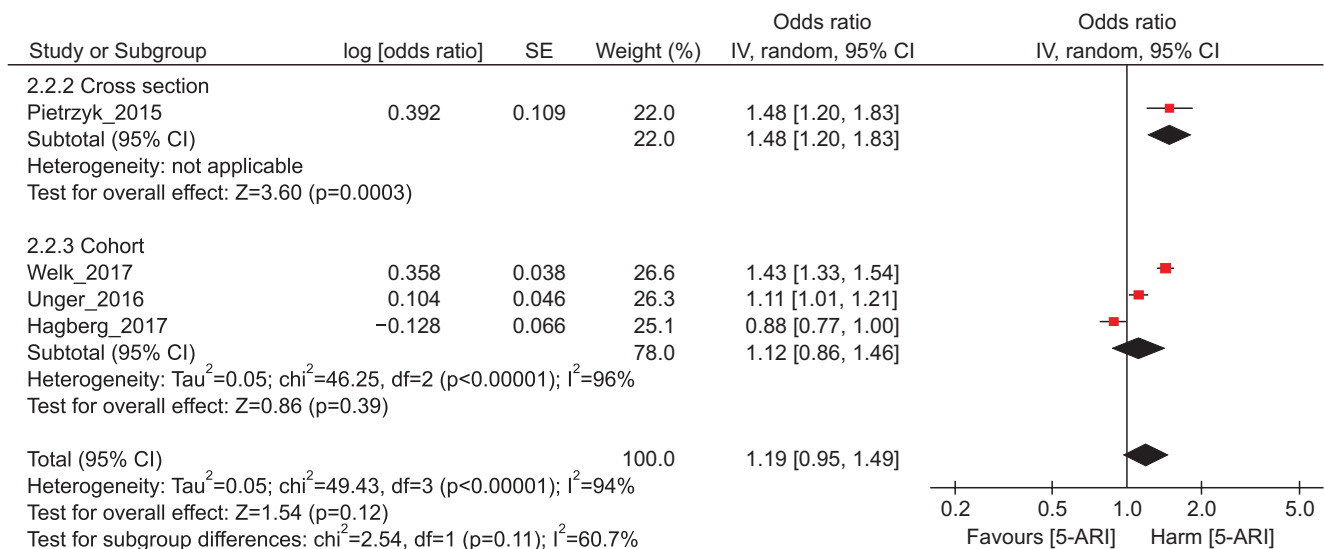


Fig. 3. Odds ratio of depression among men exposed to five-alpha reductase inhibitor (5-ARI) medication. SE: standard error, CI: confidence interval, df: degree of freedom.

Using a systematic review of included observational studies, this study is suggesting two important aspects for better understanding of this issue. First, in observational studies, it is possible that patients with adverse events could discontinue 5-ARI by themselves, which could result in a lower incidence rate of depression or suicide attempts. In the large observational study of Welk et al [16], stratified HR of 5-ARI showed decreasing pattern according to time exposure for both self-harm and depression. Second, self-discontinuation of 5-ARI could prevent future events, including depression or suicide attempts, which also could result in a

lower incidence rate of depression or suicide attempts. Using these evidences from observational studies, it is hardly to interpret whether long term medication of 5-ARI has decreasing trend of depression or self-harm or this phenomenon is just originated from limited nature of observational studies. Hence, our study is suggesting the quantitative outcome of future depression risk to design further scientific investigation.

Although our study supported null hypothesis of no association between 5-ARI and subsequent depression risk, our meta-analysis showed a borderline statistical significance with its direction to depression risk.

Table 3. Effects of moderators on HR and OR

Variable	HR					OR				
	k	Coef. ^a	HR	95% CI	p-value ^b	k	Coef. ^a	OR	95% CI	p-value ^b
No. of patients	5	0.999	-	0.999–1.000	0.711	5	0.999	-	0.999–1.000	0.736
Age	5	0.962	-	0.914–1.013	0.099	5	0.936	-	0.862–1.017	0.085
Study type					0.103					0.254
Non-cohort	2		3.722	1.015–13.653		2		5.803	0.344–97.961	
Cohort	3		1.164	0.923–1.468		3		1.123	0.862–1.462	
Control group					0.599					0.499
Alpha blocker	2		1.314	0.683–2.529		2		1.133	0.681–1.885	
Non-expose	3		1.757	1.234–2.502		3		1.507	1.069–2.122	

HR: hazard ratio, OR: odds ratio, k: number of effect sizes, Coef.: coefficient, CI: confidence interval.

^aExponential regression coefficient. ^bp-values from random effect meta-regression using restricted maximum likelihood.

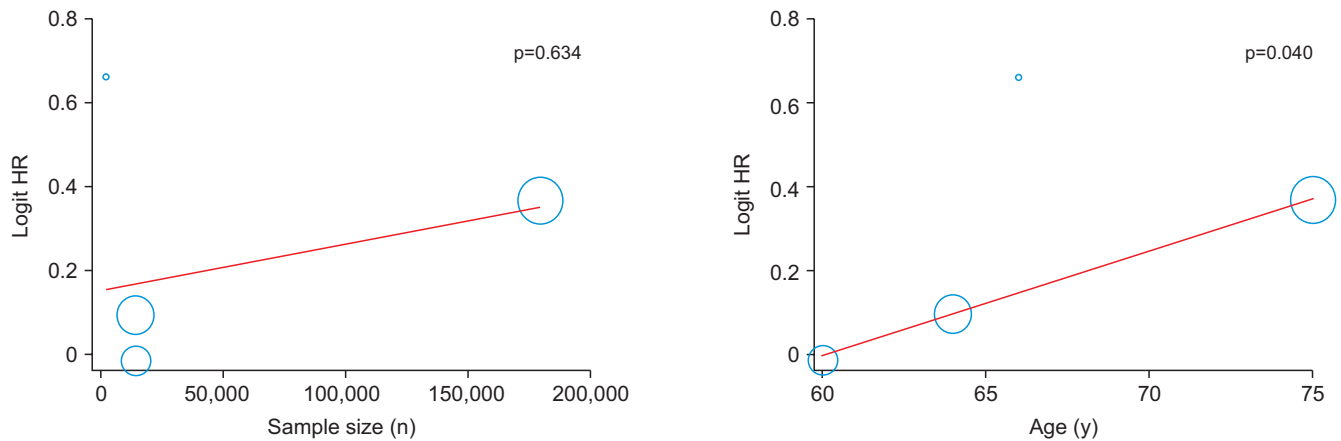


Fig. 4. Meta-regression analysis. HR: hazard ratio.

Among the studies included in qualitative analysis, one study [9] has not been considered for final quantitative analysis due to its different indication. Moreover, this study is including young population, who are far away from indicated population for this meta-analysis. If this study is included for quantitative analysis, both HR and OR are turned to be statistically significant as 1.52 (95% CI, 1.17–1.98) and 1.33 (95% CI, 1.02–1.72) (Supplement 2, 3).

To date, only limited evidence exists, with conflicting results, about the association between the use of 5-ARI and depression or suicide attempts. Recently, Welk et al [16] reported the association between the use of 5-ARI and depression or suicide attempts using their large retrospective cohort, including approximately 186,000 men who were more than 66 years old, which showed different results according to follow-up periods. The risk of suicide attempts was significantly elevated

only until 18 months of follow-up and not significant thereafter. However, risk of depression was significantly elevated both before 18 months or after 18 months but it showed decreasing trend after 18 months [16]. There was no difference according to type of 5-ARI. Moinpour et al [22] also demonstrated that there was no difference in risk of negative mental health using the 36-item Short Form health survey.

A secondary analysis of a large cross sectional study showed that there was a 1.5 fold increased risk of depression after 5-ARI medication [14]. Unger et al [15] used secondary analysis among RCT trials and found that there was a significant risk of depression after finasteride medication, of which HR was 1.10 (95% CI, 1.01–1.19). Irwig [9,10] reported that there were significantly higher rates of depression and suicidal aspect among patients with persistent sexual adverse events after discontinuation of finasteride than among con-

trols. In our study, pooled overall HR for depression risk was 1.23 (95% CI, 0.99–1.54) in random effect model, and pooled overall OR for depression risk was 1.19 (95% CI, 0.95–1.49) in random effect model.

The pathophysiology to explain the association between 5-ARI and depression has been introduced previously, including the role of 5-ARI in synthesis of several important endogenous regulating neuroactive steroids and in modulation of the neuroendocrine stress response [23]. Depression is associated with dysregulation of those important bioactive regulation steroids and with decreased androgen activity [7]. In several population-based studies, positive association between cognitive function and androgen have been revealed in both genders [24,25].

Our study has several limitations. First, most of the included studies are of observational design; hence, our meta-analysis result could also be affected by the limitative nature of the observational studies. In observational studies, defining primary outcomes, including depression or suicide attempts could be over diagnosed or underdiagnosed. Moreover, important confounders, including pre-existing psychological disorders or family history or sociodemographic features could not be adjusted [9,26]. However, most included studies are large scaled data from administrative dataset which could yield accurate power and methodological quality. Second, during meta-analysis, there was a high heterogeneity due to the inconsistent definition of depression according to each study. Third, this study could not provide quantitative risk of suicide outcomes including suicidal thought or suicidal event in association with the use of 5-ARI medication due to limitative data synthesis. Fourth, men with BPH are given a dose 5 times higher, tend to be older and may have their own confounding reasons to become depressed as they age. Moreover, this study could not determine cumulative effect of 5-ARI due to limited information from included studies.

CONCLUSIONS

Our study shows the quantitative risk of depression after 5-ARI medication using meta-analysis for first time, by which we determined the risk to be not significantly high. However, due to limited included studies, this result has to be interpreted with caution for clinical importance in real practice. However, with this

quantitative risk and its direction for depression risk, patients could be better informed during the process of shared decision making. It could also provide useful information to design a future prospective study about this issue.

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Conflicts of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: JHK, BIC. Funding acquisition: JHK. Methodology: SRS, YK. Supervision: BIC. Writing—original draft: JHK. Writing—review & editing: all authors.

Supplementary Materials

Supplementary materials can be found *via* <https://doi.org/10.5534/wjmh.190046>.

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