Use of antihypertensive drugs and risk of malignant melanoma: A meta-analysis of observational studies

Running title: Antihypertensive drugs and MM risk

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Abstract

Introduction Several antihypertensive drugs are photosensitizing and may promote the development of malignant melanoma (MM), but evidence remains inconsistent. We sought to quantify the association between use of antihypertensive drugs and MM risk.

Methods We systematically searched Pubmed, Embase, and CENTRAL from inception to August 17, 2017 to identify observational studies that reported the MM risk associated with the use of antihypertensive drugs. A random-effects meta-analysis was used to estimate the odds ratio (OR) with 95% confidence interval (CI).

Results Overall, we included eight observational studies (two cohort studies and six case-controlled studies). Compared with non-use, use of diuretics (OR, 1.10; 95% CI, 1.03 to 1.17) or beta-adrenergic blocking agents (OR, 1.19; 95% CI, 1.04 to 1.37) was significantly associated with increased risk of MM. The use of angiotensin converting enzyme inhibitors (OR, 1.08; 95% CI, 0.95 to 1.23), angiotensin II receptor blockers (OR, 1.12; 95% CI, 0.95 to 1.31), and calcium channel blockers (OR, 1.12; 95% CI, 0.72 to 1.74) was not significantly associated with increased risk of MM.

Conclusions Current evidence from observational studies suggests that use of diuretics or beta-adrenergic blocking agents may be associated with increased risk of MM. Further large well-conducted prospective studies are required to confirm our findings.

Key points

- Epidemiologic studies reported conflicting results on possible associations between use of antihypertensive drugs and risk of malignant melanoma (MM).
- Current evidence from observational studies indicates that use of diuretics or β-blockers may be positively associated with MM.
- Further large prospective studies with dose- or time-response analysis and clear adjustment for confounders are warranted.

1 Introduction

Skin cancers are the most common human cancers, mainly caused by exposure to ultraviolet radiation (UVR) [1, 2]. However, their incidence is still increasing worldwide [3], despite growing awareness of the harmful effects of sun exposure [4]. It is estimated that more than 8,500 people in the United States are diagnosed with skin cancer every day [5]. Malignant melanoma (MM), the most serious skin cancer, accounts for less than 1% of skin cancer cases, but is responsible for most skin cancer deaths [6]. Several risk factors, such as UVR exposure, number of melanocytic nevi, familiar history, and genetic susceptibility, have been proposed to explain the incidence of MM [7]. Recently, some evidence indicated that drug use might be associated with increased risk of MM [8, 9].

Antihypertensive drugs have been widely used to treat hypertension as well as other conditions including heart failure and arrhythmias [10]. It is estimated that about one-third of U.S. adults suffer from hypertension [11] and are likely to take antihypertensive drugs. However, several antihypertensive drugs are described as photosensitizing and may act as co-carcinogens with UVR to promote MM development [12]. Among the five major classes of antihypertensive drugs – angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), beta-adrenergic blocking agents (β-blockers), calcium channel blockers (CCBs), and diuretics, use of diuretics was found to be associated with an increased risk of MM in some studies [12, 13]. Similarly, a positive association was also detected between use of β-blockers and risk of MM [9, 14]. On the other hand, some studies did not find a positive association between either diuretics [9, 14] or β-blockers [15] and risk of MM. These inconsistent findings might

result from the small sample size and varieties in study durations and study populations in individual reports. Little is known about the risk of MM among individuals taking ACE inhibitors, ARBs, or CCBs. Moreover, there has been no previous systematic review and meta-analysis of the association between use of antihypertensive drugs and risk of MM. We therefore sought to conduct this meta-analysis to determine whether any of the above five major classes of antihypertensive drugs was associated with MM risk.

2 Methods

2.1 Search strategy and study selection

The electronic databases including PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched to identify observational studies (cohort and case-control studies) that evaluated the association between exposure to antihypertensive drugs and risk of MM. All of the databases were searched from inception to August 17, 2017 using combined terms (**Supplementary file 1**) without any restriction. In addition, the reference lists of relevant reviews and meta-analyses were also checked to identify additional studies.

After excluding duplicate citations, two reviewers (HT and SF) independently reviewed titles and abstracts of remaining studies to identify potential studies, which were further evaluated by retrieving their full texts. We included the studies that fulfilled the following inclusion criteria: 1) use of any antihypertensive drug as the exposure and no use of particular antihypertensive drug as the reference; 2) reported the outcome of MM; 3) reported the odds ratio (OR), relative risk (RR), hazard ratio (HR), or relevant estimates with 95% confidence intervals (CIs) or sufficient data to determine 95% CIs; and 4)

observational studies including cohort studies or case-control studies. We searched above databases without any language restriction and included papers published in other languages. Of the potential studies, none was published in a language other than English. For multiple studies using the same populations, only the study with latest or longest follow-up was included. If the article included multiple sample from different database and reported their outcomes separately, we considered it as multiple studies. We excluded abstracts and unpublished studies due to limited information to assess quality. Furthermore, to prevent double-counting from duplications, two reviewers (HT and SF) double checked the data source and populations of the included studies.

2.2 Data extraction and quality assessment

Two reviewers (HT and SF) independently extracted data and assessed the quality of each study. We collected the following information: study design, data source, number of participants, age (years), gender (%), selection criteria, exposure definition, reference definition, adjusted covariates, and the adjusted estimates. We also extracted data for further dose/time response analyses. In addition, we assessed the quality of studies according to Newcastle-Ottawa quality-assessment scale (NOS) [16], which ranges from 0 to 9, with a higher score indicating better quality. In case of any missing information, we contacted the original author for clarification. Any disagreements were resolved by consensus or referral to a third reviewer (JH).

2.3 Statistical analysis

Due to similarities among these effect measures (HR, RR, and OR) when the number of events is low (< 5%) [17], ORs with 95% CIs were used to pool the outcome data in

random-effects models. P values < 0.05 were considered statistically significant. Heterogeneity was quantified using the I^2 statistic, with I^2 of < 25%, ≥ 25% and < 75%, and ≥ 75% indicating low, medium, and high heterogeneity, respectively [18]. Separate analyses were carried out for each class of antihypertensive drug. Furthermore, additional analyses were performed if there were sufficient data (at least six studies included [19]). A subgroup analysis was performed by type of design, region of study, effect measure, and study quality to examine the source of heterogeneity. To present the development of evidence, we performed a cumulative meta-analysis based on data of publication to determine the year in which the association became significant. A sensitivity analysis was carried out to evaluate the effect of each study on the overall estimate by removing one study at a time. In addition, publication bias for risk of MM was assessed using Begg's and Egger's tests. All statistical analyses were performed with STATA (Version 14; Stata Corp., College Station, TX).

3 Results

Of 3360 citations retrieved from electronic databases, eight observational studies, i.e., two cohort studies [13, 20] and six case-control studies [9, 12, 14, 15, 21-23],met the eligibility criteria and were included in our meta-analysis (**Fig. 1**). The main characteristics of the included studies are presented in **Table 1**. Studies were published between 1996 and 2017. Six studies were carried out in Europe and two in the United States. Diuretics were used in six studies, ACE inhibitors in four studies, ARBs in three studies, β-blockers in three studies, and CCBs in two studies. OR was reported in five studies as an effect measure, incidence rate ratio (IRR) was reported in two studies, and RR was reported in one study. The included studies were of moderate or high

quality: Four were assessed as high quality with a NOS score 8 out of 9, and the remaining studies were assessed as medium quality, with scores from 5 to 7 (**Supplementary Table 2**).

3.1 Diuretics and risk of MM

The pooled estimates of six studies showed that use of diuretics was associated with significantly increased risk of MM compared with non-use (OR, 1.10, 95% CI, 1.03 to 1.17), with no evidence of heterogeneity (I^2 = 0%) (**Fig. 2**). Subgroup analyses by study design, region of study, quality of study, and effect measure were performed and the results presented in **Supplementary Table 3**. A significantly increased risk of MM was identified in studies performed in European populations (OR, 1.10; 95% CI, 1.03 to 1.17), studies with high quality (OR, 1.09; 95% CI, 1.02 to 1.17), and studies reporting IRR as an effect measure (OR, 1.12; 95% CI, 1.03 – 1.21). Our cumulative meta-analysis indicated that an increased risk of MM had been evident since 2008 (OR, 1.18; 95% CI, 1.01 to 1.39) (**Fig. 3**). Sensitivity analyses excluding one study at a time showed that no study significantly affected the overall estimates (**Supplementary Fig. 1**). There was no evidence of publication bias based on Egger's test (P = 0.18) and Begg's test (P = 0.26).

3.2 β-blockers and risk of MM

Three studies reported data on the association between β-blockers and risk of MM. When we pooled analysis of these studies, we found a significantly increased risk of MM (OR, 1.19; 95% CI, 1.04 to 1.37), with low evidence of heterogeneity (I^2 = 11.0%)

(**Fig. 2**). However, further analysis (e.g., subgroup analysis) was hampered due to the limited number of studies included.

3.3 Other classes of antihypertensive drugs and risk of MM

We identified positive associations between other classes of antihypertensive drugs and risk of MM, but they did not reach statistical significance (**Fig. 2**). For ACE inhibitors, the OR for risk of MM was 1.08 (95% CI, 0.95 to 1.23) in a pooled analysis of the data from four studies. There was low evidence of heterogeneity (I^2 = 3.4%). Three studies reported the risk of MM associated with ARBs, and their pooled analysis showed that OR for the risk of MM was 1.12 (95% CI, 0.95 to 1.31), with no evidence of heterogeneity (I^2 = 0%). The OR between CCBs and risk of MM was 1.12 (95% CI, 0.72 to 1.74), based on data from two studies, but significant heterogeneity was found (I^2 = 52.6%).

3.4 Dose/time-response analyses

One study identified a trend of an increase in risk of MM among the users of indapamide (one type of diuretic) only, with an increase in IRR from 3.85 (95% CI, 1.47 to 10.1) in a ≥ 1 year latency to 6.06 (95% CI, 1.78 to 20.7) in a ≥ 5 year latency [12]. One study found that the long-term use of ARBs, ACE inhibitors, β-blockers, and CCBs was associated with increased risk of MM, but not short term use [14]. However, the study by Koomen *et al.* did not detect either a dose or time-response for ACE inhibitors or ARBs [21].

4 Discussion

Our meta-analysis of eight observational studies involving a large overall number of participants and incident cases of MM provides evidence that use of diuretics or β-blockers is associated with a slight increase in the risk of MM. No significantly increased risk of MM was observed among patients using other classes of antihypertensive drugs (including ACE inhibitors, ARBs, and CCBs). For diuretics, our cumulative meta-analysis indicated that use was significantly associated with an increased risk of MM start in 2008. In addition, a significantly increased risk of MM was identified in studies performed in Europe, high quality studies, and studies reporting IRR as an effect measure. There was no evidence of publication bias. However, our results should be interpreted with caution due to the limited number of studies included.

The first-line treatment for hypertension usually involves diuretics [24]. It is estimated that in 2004, about one-third of patients in the United States visiting a physician to address hypertension were prescribed diuretics [25]. Among antihypertensive drugs, diuretics carry the highest risk of photosensitivity reactions [26]. However, despite the wide use of diuretics, little attention has been paid to the possible associated risk of MM. There is some evidence that a photosensitizing reaction followed by sun exposure may increase the likelihood of sunburn and photo-damage, which increases risk of MM [27]. It is well known that drug-induced photosensitivity may act as a co-carcinogen with UVR to promote MM development [12]. Some epidemiologic studies have found increased risk of MM associated with diuretics [12, 13, 20]. Consistent with those findings, our results from this meta-analysis showed that use of diuretics was significantly associated with increased risk of MM. Furthermore, our stratified analysis indicated a significantly increased risk of MM in European populations, but not in US

populations, though this might be caused by the limited number of patients included in our meta-analysis. However, our meta-analysis did not differentiate further among diuretics, and not all diuretics had the same propensity to induce photosensitivity [28]. Jensen et al. observed a trend of an increase in risk of MM among the users of indapamide, but not other diuretics [12].

It was interesting to find some evidence indicating a slightly increased risk of MM among patients taking β-blockers. Some β-blockers (e.g., sotalol) were considered photosensitizing [29], and therefore might increase MM development by acting as co-carcinogens with UVR. In a population based, matched case-control study from southern Sweden, Westerdahl *et al.* found a 70% increased risk in patients who used β-blockers as compared with non-users [9]. Recently, one population-based case-control study performed in northern Denmark found a weak association between use of β-blockers and risk of MM [14]. However, due to the limited number of studies we included, whether the weak association may be caused by chance influenced by confounders or represents a true association needs to be further investigated.

We found some evidence suggestion of increased risk of MM associated with other classes of antihypertensive drugs (ACE inhibitors, ARBs, and CCBs), but the associations were not statistically significant, which might be caused by our limited sample. Additionally, one study found that long-term use of ACE inhibitors, ARBs, β-blockers, or CCBs was associated with increased risk of MM [14]. However, little is known about the possible mechanisms underlying any carcinogenic risk associated with other classes of antihypertensive drugs. An explanation might be that some antihypertensive drugs have been reported to elicit photosensitivity and phototoxicity,

which might mediate an increased risk of MM associated with UVR [14]. However, we did not find a consistently increased risk of MM across these classes of antihypertensive drugs, which might be related to the fact that photosensitizing effects differed based on drug classes or pathways involved. In contrast, some evidence from both experimental and epidemiologic studies indicated some chemopreventive effects of ACE inhibitors and ARBs against cancer, with possible mechanisms of action including inhibition of matrix metalloprotease activity, reduced expression of vascular endothelial growth factor, and interference with the renin-angiotensin system [30]. In our meta-analysis, the use of ACE inhibitors or ARBs did not seem to protect against the development of MM, which was consistent with published observational studies [13-15, 21]. Therefore, further large well-conducted studies involving dose-response analyses are required to clarify the MM risk among these classes of antihypertensive drugs.

Our study has two strengths. First, we systematically searched electronic databases to include all relevant studies. It is important to note that this is the first meta-analysis to address the association between antihypertensive drugs and risk of MM. Second, to confirm the robustness of our findings, pre-specified subgroup analysis and sensitivity analysis were performed. We also acknowledge that our meta-analysis has several limitations. First, common risk factors for MM, such as sun exposure, ethnicity, and smoking status could not be adjusted for in the subgroup analysis, due to inconsistent control for potential confounders from included studies. Second, one potential confounder, health seeking behavior, may lead to detection bias. Individuals under hypertension management may be more likely to seek medical advice and be subject to increased surveillance, which may increase probability of disease diagnosis. However,

we did not detect an increased risk of MM across all classes of antihypertensive drugs, which suggested that the increased risk might not be entirely due to increased scrutiny. Third, of the studies we analyzed, only one (Koomen et al 2009) provided the information on cumulative doses or cumulative durations [21], which prevented us from performing a further dose-response analysis or time dependency analysis. Finally, due to the limited number of studies included, our results for ACE inhibitors, ARBs, β-blockers, and CCBs were inconsistent and therefore hinder any firm conclusions.

5 Conclusions

Our meta-analysis indicates that use of diuretics or β-blockers may be associated with increased risk of MM. There was little evidence supporting increased risk of MM with other classes of antihypertensive drugs (ACE inhibitors, ARBs, and CCBs). Further large well-conducted prospective studies with dose- or time-response analyses and clear adjustment for confounders are required to confirm our findings.

Compliance with Ethical Standards

Ethical approval and patient consent were not required for this study.

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Conflict of interest Huilin Tang, Shuangshuang Fu, Suodi Zhai, Yiqing Song, and Jiali Han have no conflicts of interest that are directly relevant to the content of this study.

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Table 1 Characteristics of included studies

Study	Study design	Data source	Duration (years)	No. of participants	Age (years)	Men (%)	Selection criteria	Exposure definition	Reference definition	Measure	Covariate adjustment
Westerdahl et al. 1996 [9]	Case-control study	Regional Tumor Registry in Southern Sweden; 1988 to 1990; Sweden	NR	MM: 348; Control: 560	15-75	46.6	Participants aged 15-75 years and diagnosed with MM, two healthy controls matched by sex, age	Diuretics; β-blockers	Never use of the particular drug class	OR	History of sunburns and host factors
Rosenberg et al. 1998 [15]	Case-control study	Hospitals in Baltimore; 1983 to 1996; US	3.8	MM: 597; Controls: 6492	54	NR	Patients with MM and selected controls aged 40-69 years	CCBs; β-blockers; ACEi	Never use of the particular drug class	RR	Age, interview year, body mass index, race, and years of education, etc.
Jensen et al. 2008 [12]	Case-control study	Danish Cancer Registry; North Jutland County; 1989 to 2003; Denmark	NR	MM: 1010; BCC: 594; SCC: 1129; Controls: 32,412	NR	NR	Patients registered with a first primary diagnosis of BCC, SCC, or MM, and four population controls selected for each case	Diuretics	Never use of diuretics	IRR	Prior hospitalization for selected chronic diseases and use of glucocorticoids.
Koomen et al, 2009 [21]	Case-control study	PHARMO linkage network and the PALGA database; 1991 to 2004; Netherlands	≥ 3	MM: 1272; Controls: 6520	55	40	Patients with primary MM between 1991 and 2004, aged ≥18 years and having 3 years of follow-up prior to diagnosis, and	ACEi or ARB for at least six months	Non exposed to particular drug class	OR	Total number of unique medical diagnoses and the use of statins

							matched controls				
De Vries et al. 2012 [22]	Case-control study	Multicenter, hospital-based, case–control study was carried out in Finland, Germany, Greece, Italy, Malta, Poland, Scotland and Spain; NR; Europe	NR	MM:360; SCC:409; BCC:602; Controls:1550	67	56	Patients recently diagnosed with SCC, BCC, or MM (≥18 years) and matched controls	Thiazide diuretics at least for 3 months	No use for more than 3 months	OR	Age, sex, phototype, and country
Schmidt et al. 2015 [14]	Case-control study	Northern Denmark using various registries linked by the CPR numbers; 1991 to 2010; Denmark	Maximize: 19	SCC: 2,282; BCC:17, 242, MM:3,660; controls: 231,743	67	46	Aged ≥20 years with a first-time diagnosis of SCC, BCC, or MM and 10 matched controls	B-blockers, ACEi, ARBs, CCBs, or diuretics for > 2 prescriptions before the index date	Non-users with ≤ 2 prescriptions of any antihypertensive drug	OR	CCI score, hospital-diagnosed obesity, and use of systemic glucocorticoids, aspirin, non-aspirin NSAIDs, and statins
Kaae et al. 2010 [20]	Cohort study	Danish national registers;1995 to 2006; Denmark	NR	4,761,749 participants	NR	NR	Patients identified from Danish Cancer Registers filled at least one prescription for photosensitizing medication	Diuretics	Never users of diuretics	IRR	Age, period, sex, and education

Nardone et al. 2017 [13]	Cohort study	Northwestern Medicine Enterprise Data Warehouse; 2004 to 2015; US	4	ACEi: 27,134, Control: 81,399; ARBs:1 3,818, Control: 41,454; Thiazides: 15,166, Control: 45,498	NR	43.4	Patient age range 18-89 years, one or more written orders for an ACEi, ARB, or thiazides; 3 matched individuals with no documented order for any antihypertensive drug	ACEi, ARB, or thiazides	Non exposed to particular drug class	OR	Age, gender, race, and CCI

ACEi angiotensin converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *BCC* basal cell carcinoma, *β-blockers* beta-adrenergic blocking agents, *CCBs* calcium channel blockers, *CCI* charlson comorbidity index, *IRR* incidence rate ratio, *MM* malignant melanoma, *NR* not reported, *NSAID* non-steroidal anti-inflammatory drug, *OR* odds ratio, *RR* relative risk, *SCC* squamous cell carcinoma

Figure legends:

Fig. 1 Flow chart of the identification of eligible studies

Fig. 2 Meta-analysis of the association between use of antihypertensive drugs and risk of malignant melanoma. Definitions of exposure and reference are presented in Table 1*ACE inhibitors* angiotensin converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *β-blockers* beta-adrenergic blocking agents, *CCBs* calcium channel blockers, *CI* confidence interval, MM malignant melanoma

Fig. 3 Cumulative meta-analysis of studies ordered by year of publication for the association between use of diuretics and risk of malignant melanoma. The studies are added at one time according to year of publication and the results are summarized as each new study is added. Definitions of exposure and reference are presented in Table 1. *CI* confidence interval, *MM* malignant melanoma

Figure 1

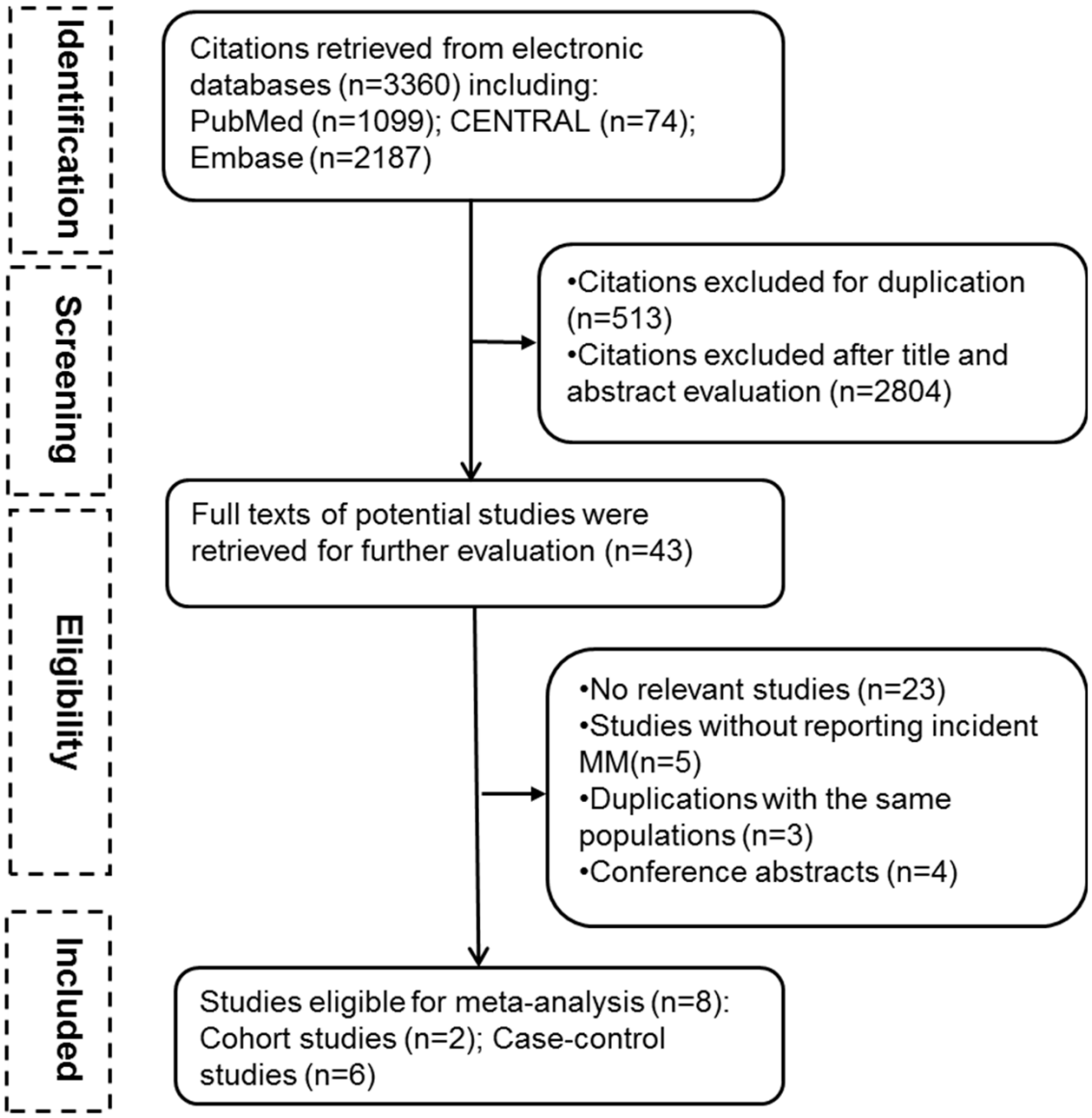

Identification
Screening
Eligibility
Included
Citations retrieved from electronic databases (n=3360) including: PubMed (n=1099); CENTRAL (n=74); Embase (n=2187)
•Citations excluded for duplication (n=513)
•Citations excluded after title and abstract evaluation (n=2804)
Full texts of potential studies were retrieved for further evaluation (n=43)
•No relevant studies (n=23)
•Studies without reporting incident MM(n=5)
•Duplications with the same populations (n=3)
•Conference abstracts (n=4)
Studies eligible for meta-analysis (n=8): Cohort studies (n=2); Case-control studies (n=6)

Figure 2

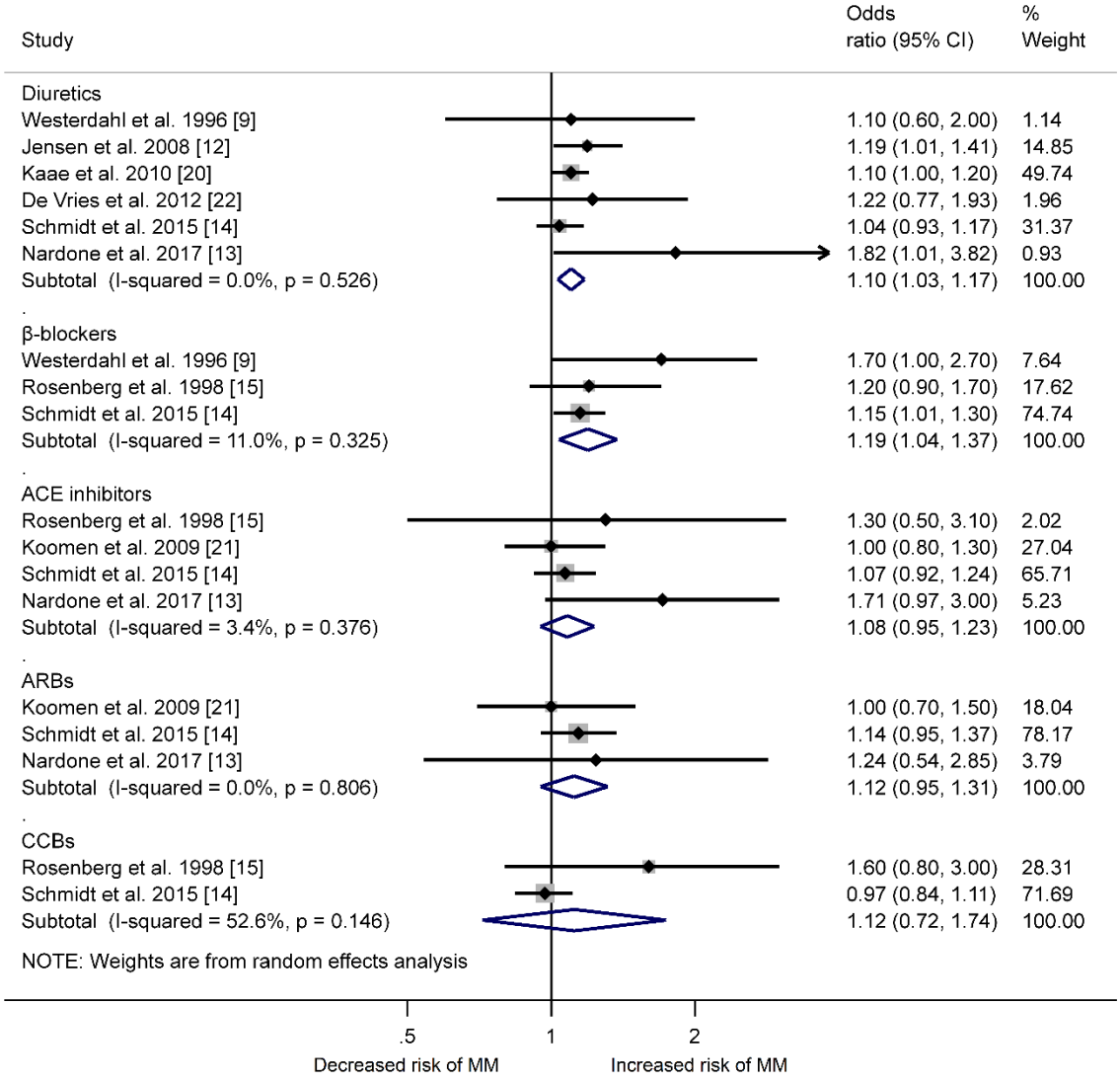
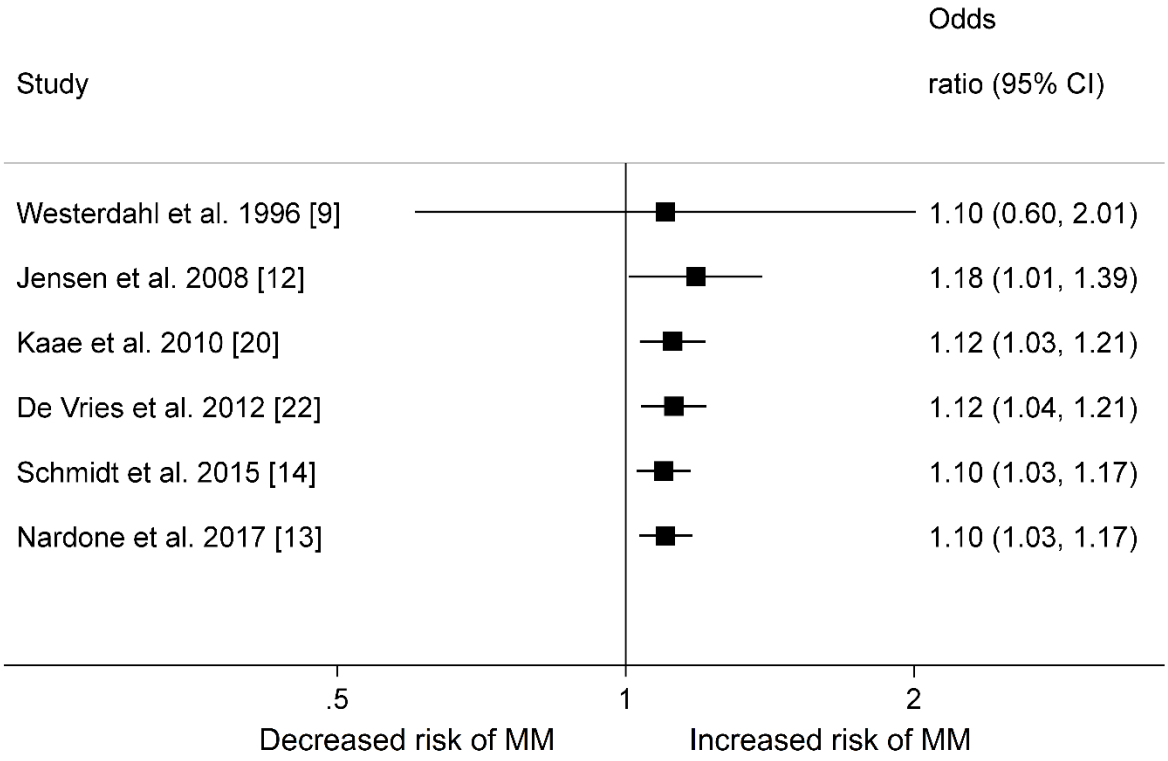

Study
Odds ratio (95% CI)
% Weight
Diuretics
Westerdahl et al. 1996 [9] 1.10 (0.60, 2.00) 1.14
Jensen et al. 2008 [12] 1.19 (1.01, 1.41) 14.85
Kaae et al. 2010 [20] 1.10 (1.00, 1.20) 49.74
De Vries et al. 2012 [22] 1.22 (0.77, 1.93) 1.96
Schmidt et al. 2015 [14] 1.04 (0.93, 1.17) 31.37
Nardone et al. 2017 [13] 1.82 (1.01, 3.82) 0.93
Subtotal (I-squared = 0.0%, p = 0.526) 1.10 (1.03, 1.17) 100.00
β-blockers
Westerdahl et al. 1996 [9] 1.70 (1.00, 2.70) 7.64
Rosenberg et al. 1998 [15] 1.20 (0.90, 1.70) 17.62
Schmidt et al. 2015 [14] 1.15 (1.01, 1.30) 74.74
Subtotal (I-squared = 11.0%, p = 0.325) 1.19 (1.04, 1.37) 100.00
ACE inhibitors
Rosenberg et al. 1998 [15] 1.30 (0.50, 3.10) 2.02
Koomen et al. 2009 [21] 1.00 (0.80, 1.30) 27.04
Schmidt et al. 2015 [14] 1.07 (0.92, 1.24) 65.71
Nardone et al. 2017 [13] 1.71 (0.97, 3.00) 5.23
Subtotal (I-squared = 3.4%, p = 0.376) 1.08 (0.95, 1.23) 100.00
ARBs
Koomen et al. 2009 [21] 1.00 (0.70, 1.50) 18.04
Schmidt et al. 2015 [14] 1.14 (0.95, 1.37) 78.17
Nardone et al. 2017 [13] 1.24 (0.54, 2.85) 3.79
Subtotal (I-squared = 0.0%, p = 0.806) 1.12 (0.95, 1.31) 100.00
CCBs
Rosenberg et al. 1998 [15] 1.60 (0.80, 3.00) 28.31
Schmidt et al. 2015 [14] 0.97 (0.84, 1.11) 71.69
Subtotal (I-squared = 52.6%, p = 0.146) 1.12 (0.72, 1.74) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
Decreased risk of MM
Increased risk of MM

Figure 3


Odds
Study
ratio (95% CI)
Westerdahl et al. 1996 [9]
1.10 (0.60, 2.01)
Jensen et al. 2008 [12]
1.18 (1.01, 1.39)
Kaae et al. 2010 [20]
1.12 (1.03, 1.21)
De Vries et al. 2012 [22]
1.12 (1.04, 1.21)
Schmidt et al. 2015 [14]
1.10 (1.03, 1.17)
Nardone et al. 2017 [13]
1.10 (1.03, 1.17)
.5
1
2
Decreased risk of MM
Increased risk of MM