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SYSTEMATIC REVIEW AND META-ANALYSIS

Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis

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BACKGROUND: Sex differences in the management of cardiovascular disease have been reported in secondary care. We conducted a systematic review with meta-analysis of systematically investigated sex differences in cardiovascular medication prescription among patients at high risk or with established cardiovascular disease in primary care.

METHODS AND RESULTS: PubMed and Embase were searched between 2000 and 2019 for observational studies reporting on the sex-specific prevalence of aspirin, statins, and antihypertensive medication prescription, including beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics, in primary care. Random effects meta-analysis was used to obtain pooled women-to-men prevalence ratios for each cardiovascular medication prescription. Metaregression models assessed the impact of age and year on the findings. A total of 43 studies were included, involving 2 264 600 participants (28% women) worldwide. Participants' mean age ranged from 51 to 76 years. The pooled prevalence of cardiovascular medication prescription for women was 41% for aspirin, 60% for statins, and 68% for any antihypertensive medications. Corresponding rates for men were 56%, 63%, and 69% respectively. The pooled women-to-men prevalence ratios were 0.81 (95% CI, 0.72–0.92) for aspirin, 0.90 (95% CI, 0.85–0.95) for statins, and 1.01 (95% CI, 0.95–1.08) for any antihypertensive medications. Women were less likely to be prescribed angiotensin-converting enzyme inhibitors (0.85; 95% CI, 0.81–0.89) but more likely with diuretics (1.27; 95% CI, 1.17–1.37). Mean age, mean age difference between the sexes, and year of study had no significant impact on findings.

CONCLUSIONS: Sex differences in the prescription of cardiovascular medication exist among patients at high risk or with established cardiovascular disease in primary care, with a lower prevalence of aspirin, statins, and angiotensin-converting enzyme inhibitors prescription in women and a lower prevalence of diuretics prescription in men.

Key Words: cardiovascular medication ■ meta-analysis ■ primary care ■ sex differences ■ systematic review

Cardiovascular disease (CVD) remains the leading cause of death worldwide, accounting for about a third of all deaths in both women and men.[1] Historically, there has been a misperception that CVD predominantly affects men, which may have resulted in suboptimal management and treatment of CVD in women.[2,3] Over recent decades, substantial efforts have been made to characterize CVD in women. As a result, important differences between women and men in the presentation, diagnosis, and medical treatment of CVD have been identified.[2,4]

Most studies on sex differences in CVD management have been performed in secondary care.[3,5–7] For example, among all patients receiving statins after hospitalization for myocardial infarction in the United States, women were less likely than men to receive high-intensity statins, despite guideline recommendations.[6] Also, a study of coronary heart

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CLINICAL PERSPECTIVE

What Is New?

- This systematic review with meta-analysis shows that there are sex differences in cardiovascular medication prescription among patients at high risk or with established cardiovascular disease in primary care.
- Women were less likely to be prescribed aspirin, statin, or angiotensin-converting enzyme inhibitor but more likely to have a prescription for diuretics.

What Are the Clinical Implications?

- Sex differences in cardiovascular prescription in primary care need to be addressed in order to optimize the use of cardiovascular medication for both women and men.

Nonstandard Abbreviations and Acronyms

ACEI	angiotensin-converting enzyme inhibitors
Antihtn	antihypertensive medications
BB	beta blocker
CCB	calcium channel blocker
CHD	coronary heart disease
CVD	cardiovascular disease

disease patients recruited from routine outpatient cardiology clinics in 11 countries across Europe, Asia, and the Middle East showed that women were less likely than men to reach all treatment targets set by clinical guidelines.[3] Whether similar sex differences exist in primary care has not been systematically evaluated. Considering that both patients at high risk and with established CVD attended clinics in primary care to monitor their current CVD treatment, primary care visits are a key stage at which any sex inequities in treatment could and should be investigated. Comprehensive evidence on current sex differences in cardiovascular medication prescription in primary care would help to obtain a better understanding of the utilization of evidence-based medical treatment for both sexes and encourage all health professionals to strive for sex equity in providing CVD management to their patients.

In this study, we conducted a systematic review and meta-analysis to determine the prevalence of common cardiovascular medication prescription in women and men in primary care and to evaluate whether prescriptions for guideline-recommended cardiovascular medications differ between the sexes.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Search Strategy

A systematic search of observational studies was performed in PubMed/MEDLINE and Embase for studies published between 2000 and 2019 using combined text word subject heading terms (Table S1). The reference lists of all related articles were screened for any other potentially relevant studies.

Study Selection and Data Extraction

All observational studies that reported the sex-specific prevalence of prescriptions of cardiovascular medications (aspirin, statins, and any antihypertensive medication including beta blockers, calcium channel blockers [CCBs], angiotensin-converting enzyme inhibitors [ACE inhibitors], and diuretics) for patients at high risk or with established CVD (coronary heart disease, stroke, heart failure, and atrial fibrillation) in primary care were included. Studies were excluded if they (1) were published in a language other than English; (2) presented an unrelated study population, outcome, or were not performed in primary care; (3) included <1000 patients; (4) reported cardiovascular medication prescription only for 1 sex; and (5) assessed cardiovascular medication not by prescription (such as self-report or pharmacy dispensing).

Duplicate records were removed before title and abstract screening. When there were multiple reports from the same study, the report involving the highest number of cases or most explicit participants characteristics and outcome measures was included. Four independent reviewers (M.Z., E.R.C.M., C.C., and K.H.) screened the papers by title and abstract against the inclusion and exclusion criteria. Any disagreement between reviewers was discussed and the full text was reviewed, if necessary. A similar process took place in reviewing the full text of selected papers. A tailor-made data extraction form was used to collect information on study and participant characteristics and sex-specific prevalence of prescriptions of cardiovascular medication (Table S2).

Quality Assessment

Study quality was assessed using the modified Newcastle-Ottawa scale for observational studies.

This scale consists of 6 items that assess the quality of participant selection, comparability, and outcome adjudication (Tables S3 and S4).[8]

Outcomes

The primary outcome was the women-to-men prescription prevalence ratio with 95% CI for each cardiovascular medication. The secondary outcomes were the sex-specific prescription rates of each cardiovascular medication.

Statistical Analysis

In general, the included studies reported unadjusted numbers, rates, or percentages of women and men with cardiovascular medication prescriptions. If a measure of variability was not reported, these were estimated from the rate and the sample size. The women-to-men prevalence ratios with 95% CI were pooled across studies using random-effects meta-analyses with inverse-variance weighting for each medication.[9] In sensitivity analysis, we pooled the results from studies that had adjusted for age. As different studies reported on different antihypertensive medications, we also restricted the analyses on individual antihypertensive medications to studies that reported on each of the 4 antihypertensive medications. Metaregression analyses were performed to assess the impact of mean age and age difference (women minus men) on our findings. We further investigated whether there was a trend in sex differences in cardiovascular medication prescription over time. In subgroup analysis, we assessed whether the findings differed by CVD status (high risk only, prevalent CVD, and high risk and prevalent CVD combined). $P<0.05$ were considered statistically significant. Statistical analyses were performed by using the "metafor" package in R version 3.2.2.

RESULTS

Study Characteristics

Of the 10 803 studies identified through the systematic search, 900 studies were reviewed in full text (Figure 1). Of these, 43 studies were included, including a total of 2 264 600 participants, of whom 630 111 (28%) were

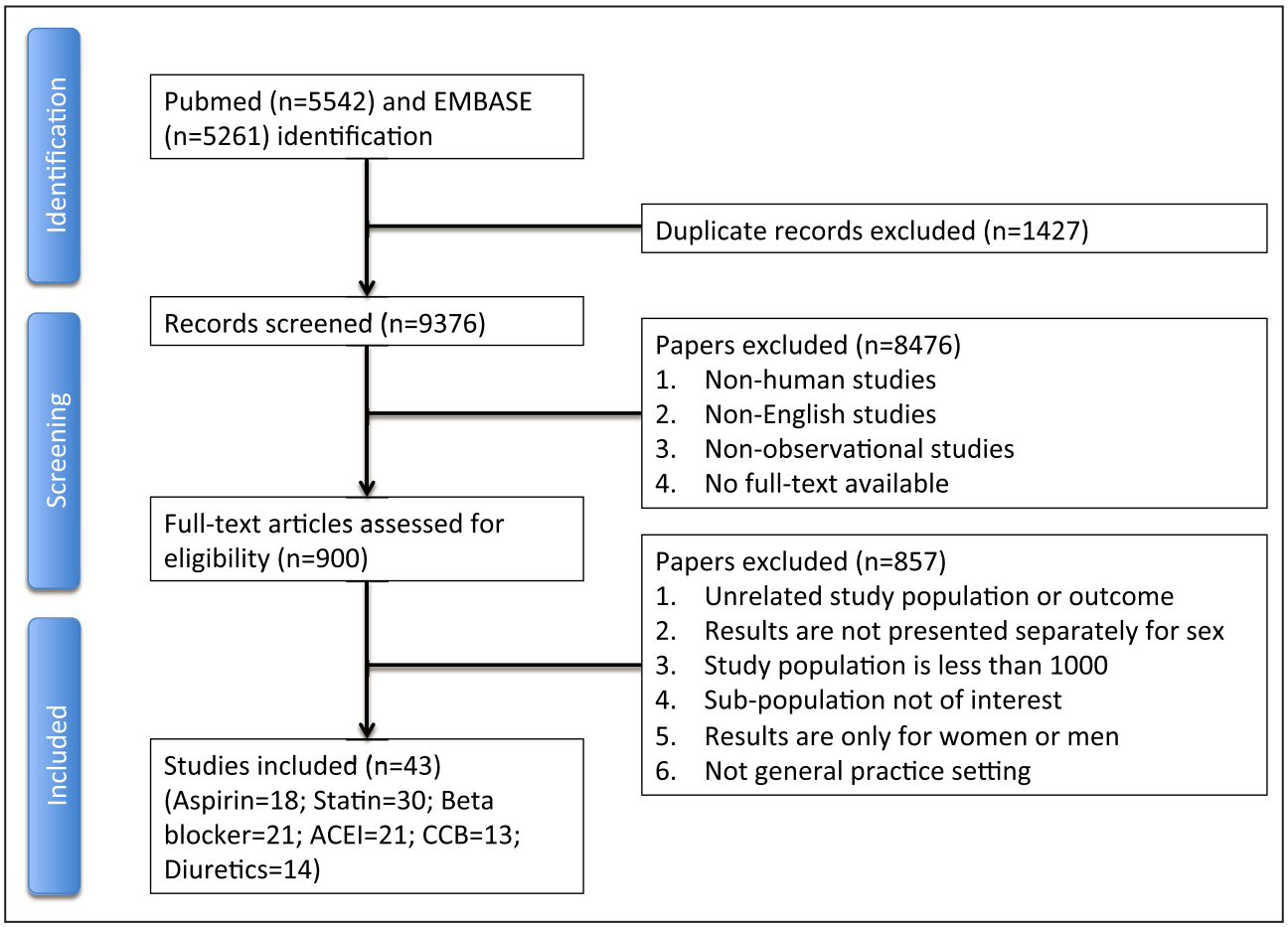

Figure 1. Flowchart of records screened and included in the systematic review.
ACEI indicates angiotensin-converting enzyme inhibitor; and CCB, calcium channel blocker.

women. The mean age ranged from 51 to 76 years (where reported). Table shows the key characteristics of the included studies. Of the 43 studies, 18 included information on aspirin,[10–27] 30 on statins,[*] 14 on any antihypertensive medications,[†] 21 on beta blockers,[‡] 13 on CCBs,[§] 21 on ACE inhibitors,[‖] and 14 on diuretics.[¶] Eight out of 43 studies reported cardiovascular medication prescription for high-risk patients,[17,32,38,47–49,52,53] 24 for patients with established CVD,[#] and 11 for both high-risk and CVD patients.[**]

Sex Differences in Prevalence of Cardiovascular Medication Prescription

In women, the pooled prevalence of cardiovascular medication prescription was 41% for aspirin, 60% for statins, and 68% for overall antihypertensive medications. The corresponding rates for men were 56%, 63%, and 69%, respectively. The pooled women-to-men prevalence ratios were 0.81 (95% CI, 0.72–0.92) for aspirin, 0.90 (95% CI, 0.85–0.95) for statins, and 1.01 (95% CI, 0.95–1.08) for any antihypertensive medications (Figure 2).

Figure 3 shows the women-to-men prevalence ratios of individual antihypertensive medication prescription. Women were less likely to be prescribed with ACE inhibitors (women-to-men prevalence ratio: 0.85; 95% CI, 0.81–0.89) whereas the prevalence of diuretics prescription was higher than in men (women-to-men prevalence ratio: 1.27; 95% CI, 1.17–1.37). There were no significant sex differences in the prescription of beta blockers and CCBs. Findings were similar in analyses restricted to studies that reported on all 4 individual antihypertensive medications (Figure S1). Findings were similar in age-adjusted analyses, available for 31 studies (Tables S5 through S10).

Impact of Age on the Sex Differences in Prevalence of Cardiovascular Medication

Among the 31 studies that reported a sex-combined mean age of the study population, there was no evidence that the women-to-men prevalence ratio varied systematically according to the mean age (Figure S2; *P* values: 0.57 for aspirin; 0.24 for beta blockers; 0.27 for CCBs; 0.41 for ACE inhibitors; 0.85 for diuretics). The only exception was that in studies with older patients, women were less likely than men to be prescribed statins whereas women had a higher prevalence of statin prescription compared with men in studies including younger patients (*P*=0.003).

Among the 17 studies that reported sex-specific mean ages, there was no evidence that the prevalence ratio varied systematically according to the women to men age difference (Figure S3; *P* values: 0.34 for aspirin; 0.21 for statins; 0.93 for beta blockers; 0.91 for CCBs; 0.89 for ACE inhibitors). The exception was the higher prevalence of diuretics prescription in women increased as the difference between the mean age of women and the mean age of men increased (*P*=0.006).

Sex Differences in the Prevalence of Cardiovascular Medication Prescription Over Time

The sex differences in prevalence ratio of prescription did not significantly change over time for aspirin (*P*=0.92), any antihypertensive medications (*P*=0.99), beta blockers (*P*=0.43), CCBs (*P*=0.44), ACE inhibitors (*P*=0.39), and diuretics (*P*=0.58) (Figure S4). However, the pattern and magnitude of the sex differences in statin prescription changed over time, with an increased women-to-men prevalence ratio (*P*=0.003).

Sex Differences in Cardiovascular Medication Prescription by CVD Status

Among patients with established CVD, women were less likely to be prescribed with aspirin (0.89, 95% CI, 0.84–0.94), statins (0.85; 95% CI, 0.80–0.90), beta blockers (0.90, 95% CI, 0.85–0.96), and ACE inhibitors (0.88, 95% CI, 0.84–0.93) (Figure S5, Table S11). In contrast, women with established CVD were more likely to be prescribed with diuretics than their male counterparts (1.25; 95% CI, 1.09–1.43). Similar pooled estimates, but with wider CIs, were found when studies included only high-risk participants, or when studies included both participants at high risk of and with established CVD. Time trends in the women-to-men prevalence ratio in medication prescription did not differ materially by CVD status (Figures S6 through S11). However, the women-to-men ratio of statin prescription increased over time in studies among high-risk patients but not in studies including patients with established CVD or in studies including both high-risk and CVD patients (*P* for interaction=0.002).

DISCUSSION

In this systematic review and meta-analysis of 43 studies including over 2 million participants, we found that there were sex differences in cardiovascular medication prescription among patients at high risk or with established CVD in primary care. Compared with men, women were less likely to have a prescription for

[*]References 11–13, 15, 19–23, 25, 26, 28–46.
[†]References 10, 17–19, 24, 25, 30, 35–38, 42, 47, 48.
[‡]References 10–13, 19–23, 25–27, 32, 34, 38, 45, 47–51.
[§]References 10–12, 21, 26, 32, 34, 38, 45, 47–49, 52.
[‖]References 10–14, 17, 19, 20, 25, 26, 32, 34, 38, 40, 45, 47–52.
[¶]References 10–12, 14, 21, 26, 32, 38, 45, 47–49, 51, 52.
[#]References 11–14, 16, 19–24, 28–31, 33–36, 39, 43, 45, 50, 51.
[**]References 10, 15, 18, 25–27, 37, 40–42, 46.

Table. Key Characteristics of Selected Studies

Study	Year	Country	Prevention Type	Sample Size	Women	Men	Age, y	Cardiovascular Medications						
								Aspirin	Statin	Antihtn	BB	CCB	ACEI	Diuretics
Al-Lawati et al[10]	2007	Oman	Mixed	2551	1352	1199	54	X		X	X	X	X	X
Alberts et al[28]	2004	Multiple	Secondary	55 499	18 315	37 184	69		X					
Brady et al[11]	1998	UK	Secondary	24 431	9898	14 533	67	X	X		X	X	X	X
Brady et al[20]	2002	UK	Secondary	12 045	4457	7588	67	X	X		X		X	X
Bull et al[31]	2003*	UK	Secondary	13 929	5827	8102	>40		X					
Carlsson et al[21]	2013*	Sweden	Secondary	7408	3330	4078	76	X	X		X	X		X
Carroll et al[22]	2001	UK	Secondary	6778	2787	3991	NA	X	X		X			
Catalán-Ramos et al[32]	2009	Spain	Primary	696 073	358 218	337 855	51		X		X	X	X	X
Crilly et al[23]	2001	UK	Secondary	1162	552	610	69	X	X		X			
Dodhia et al[33]	2013	UK	Secondary	6711	2828	4564	70		X					
Dreyer et al[34]	2007	Australia	Secondary	2005	721	1284	70		X		X	X	X	
Driscoll et al[24]	2007	Australia	Secondary	12 509	5267	7242	73	X		X				
Emberson et al[25]	2001	UK	Mixed	8538	4286	4252	NA	X	X	X	X		X	
Forster et al[35]	2013	UK	Secondary	23 811	4502	4252	NA		X	X				
Greving et al[49]	2000	NL	Primary	7550	4774	2776	63				X	X	X	X
Gulliford et al[36]	2010*	UK	Secondary	7065	3816	3249	73		X	X				
Hawkins et al[50]	2007	UK	Secondary	13 330	6803	6527	68				X		X	
Hendrix et al[26]	2005*	US	Mixed	72 508	29 208	43 300	NA	X	X		X	X	X	X
Hippisley-Cox et al[27]	2001*	UK	Mixed	5891	2783	3108	NA	X			X			
Hyun et al[37]	2012	Australia	Mixed	13 294	6202	7092	61		X	X				
Journath et al[38]	2005	Sweden	Primary	6537	3410	3127	66		X	X	X	X	X	X
Lahoz et al[12]	2008*	Spain	Secondary	8817	2319	6498	65	X	X		X	X	X	X
Law et al[44]	2010	Canada	Primary	390	128	262	58		X					
Lawlor et al[29]	2000	UK	Secondary	1314	483	831	NA		X					
Lee et al[19]	2018	Australia	Secondary	130 926	61 142	69 784	67	X	X	X	X		X	
Macchia et al[13]	2012*	Italy	Secondary	21 423	6928	14 495	NA	X	X		X		X	
Majeed et al[39]	1996	UK	Secondary	63 259	34 545	28 714	NA		X					
Majeed et al[14]	2002	UK	Secondary	2129	1224	905	NA	X					X	X
Murphy et al[51]	2004*	UK	Secondary	2186	1213	973	NA				X		X	X
Nanna et al[46]	2015	US	Mixed	5693	2460	3233	68		X					
Nilsson et al[40]	2004*	Sweden	Mixed	9375	4293	5082	65		X				X	
Nilsson et al[52]	2007*	Sweden	Primary	1135	714	421	52					X	X	X

(*Continued*)

Table. Continued

Study	Year	Country	Prevention Type	Sample Size	Women	Men	Age, y	Cardiovascular Medications					
								Aspirin	Statin	Antihtn	BB	CCB	ACEI	Diuretics
Owen et al[47]	2009*	Australia	Primary	12 499	5896	6603	63			X	X	X	X	X
Paulsen et al[48]	2011*	Denmark	Primary	5413	3305	2108	66			X	X	X	X	X
Qato et al[15]	2011	US	Mixed	4136	2233	1903	52	X	X					
Saposnik et al[30]	2004	Canada	Secondary	1094	415	679	67		X	X				
Sheppard et al[41]	2009	UK	Mixed	4699	1937	2762	54		X					
Svilaas et al[16]	2000*	Norway	Secondary	2060	707	1353	69	X						
Tabenkin et al[17]	2004	US	Primary	407	210	197	53	X		X			X	
Turnbull et al[42]	2008	Australia	Mixed	3664	1834	1830	68		X	X				
Virani et al[43]	2011	US	Secondary	972 532	13 371	959 161	71		X					
Weler et al[18]	2003	US	Mixed	3849	1953	1896	65	X		X				
Wandell et al[45]	2007	Sweden	Secondary	7975	3465	4510	NA		X		X	X	X	X

ACEI indicates angiotensin converting enzyme inhibitor; Antihtn, any anti-hypertensive medication; BB, beta blocker; CCB, calcium channel blocker; EU, Europe; NL, The Netherlands; UK, United Kingdom; and US, United States.
*Year: study performed year. Studies with asterisk indicate publication year.

aspirin, statins, or ACE inhibitors but more likely to have a prescription for diuretics. Sex differences did not vary materially by age, but there was some evidence to suggest that the magnitude of sex differences in statin prescription increased over time.

Previous studies in secondary care have demonstrated that women are generally less likely than men to have a prescription of guideline-recommended cardiovascular medications after a cardiac event.[2,3,5,54] SUrvey of Risk Factors, a clinical audit with over 10 000 patients from 11 countries, indicated that women had a lower prevalence of cardiovascular medication use than men and were less likely to reach treatment targets.[3] Similarly, a study of 36 000 patients with established coronary heart disease in the United States, showed that women were less likely than men to be prescribed with aspirin, ACE inhibitors, or statins at both acute and hospital discharge of coronary heart disease.[55] A study in the United Kingdom showed that prescription rates for cardiovascular medications were about 10% lower among women than men <55 years for acute myocardial infarction.[56] Furthermore, a Dutch population-based analysis also found persistent sex differences in the use of lipid-lowering medications for secondary prevention of CVD, particularly in younger patients.[5] We did not observe that sex disparities differed between age groups, but we noticed that the sex differences in statin prescription persisted and was even larger in the more recent studies. A recent study in the United States confirmed that women were 9% less likely than men to receive high-intensity statins, as opposed to other types of statin.[57] The present study further expands these findings by showing that sex differences in medication prescription also exist among patients at high cardiovascular risk or with established CVD in a primary care setting. We also demonstrated that women were more likely to be on diuretics but less likely to be on ACE inhibitors, which is in line with other studies.[56,58,59] Sex differences in progression and presentation of CVD and comorbidities, the efficiency of treatment, and/or adverse drug effects may lead to different requirements on antihypertensive regimens.[59,60] The reasons for the contrasting sex differences within antihypertensive medication classes require further study.

There are several other possible explanations for the lower prescription rates of some cardiovascular medications in women than men. First, the incidence of CVD in women is, typically, about a third that of men in middle age and occurs in men about a decade earlier than women, which might have led to the misperception that CVD is less common in women and does not have to be prevented as intensively as in men.[4,34,61] Additionally, women may have a lower awareness of the severity of

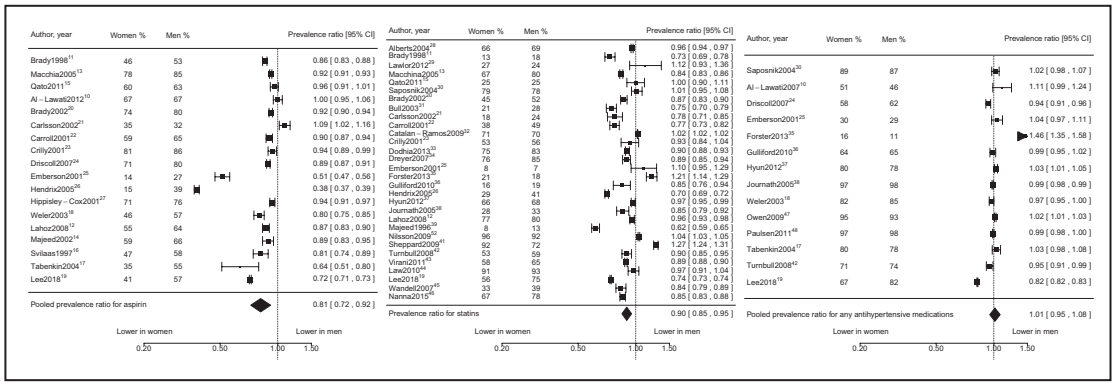

Figure 2. Women-to-men prevalence ratio of aspirin, statins, and any antihypertensive medications prescription.
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% CI. The diamond indicates the pooled summary and its 95% CI.

their disease and of appropriate CVD treatment and receive less support from healthy providers, compared with men, resulting in lower health consciousness and less frequent use of healthcare services.[5,62–64]

Although beyond the scope of the current investigation, studies have reported a considerable delay in receiving appropriate medical treatment to reduce the risk of incident or recurrent cardiac event in women.[2,23,62,63] Also, women may have less belief than men in the safety and effectiveness of cardiovascular medications and have been reported to have a greater risk of suffering adverse drug reactions, which may lead to a higher discontinuation rate of cardiovascular medications.[60,65–67] Indeed, studies have shown that women have a poorer adherence to cardiovascular medication than men in primary

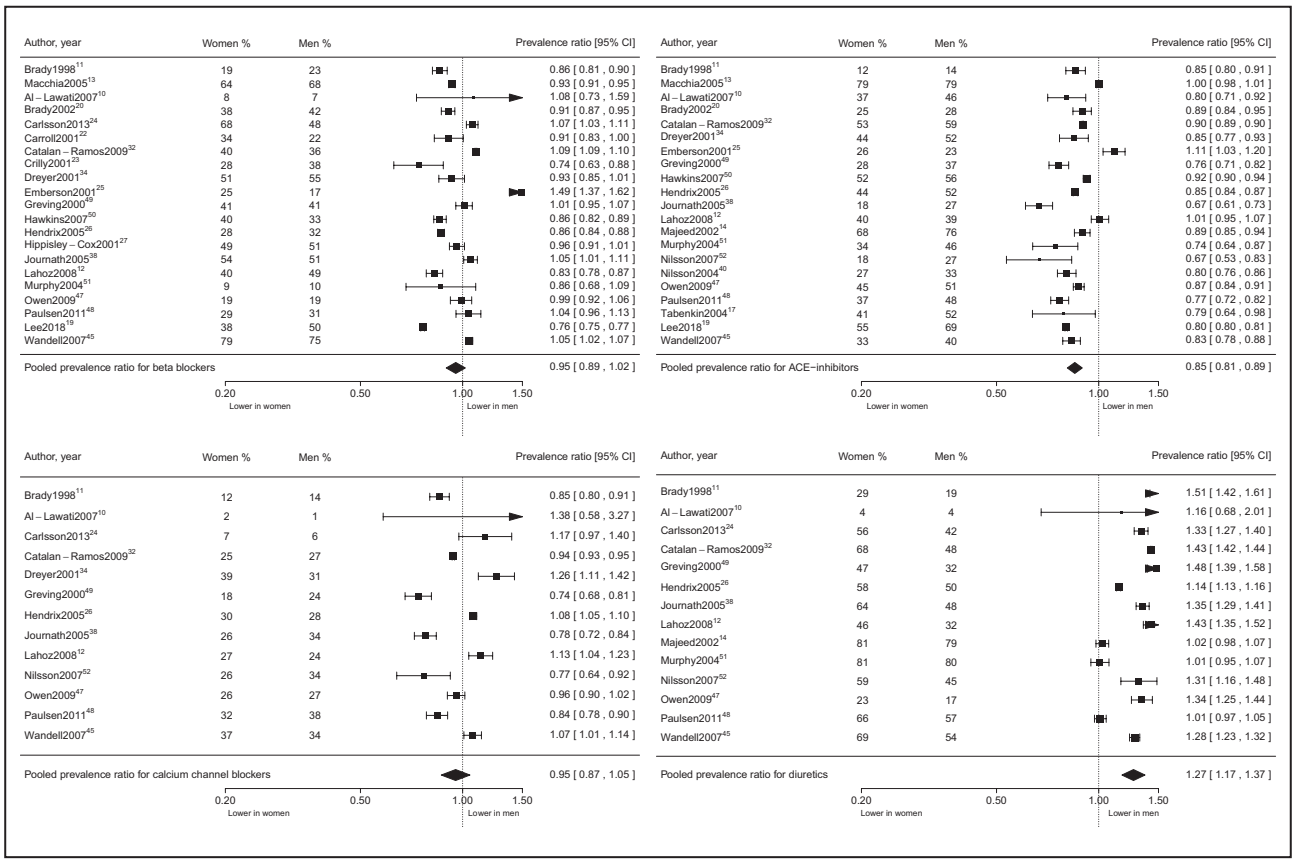

Figure 3. Women-to-men prevalence ratio of individual antihypertensive medication prescription.
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% CI. The diamond indicates the pooled summary and its 95% CI.

care.[68,69] These factors would be expected to produce a wider disparity between the usage of cardiovascular medications than our study of prescriptions suggests.

We conducted a large-scale systematic review with meta-analyses on sex differences in cardiovascular medication prescription among patients at high risk or with established CVD in a primary care setting. We included all major cardiovascular medications and found that our results were generally robust across patient characteristics. Limitations of this study are inherent to its design and include the differences across studies in design, population, and end point definition.[9] We had no information on potential combinations of cardiovascular medications prescribed, nor were we able to adjust our findings to potentially important comorbidities or other characteristics. However, some cardiovascular medications target the same risk factor and the lower use of ACE inhibitors among women, relative to men, could be explained by women's higher use of diuretics. Also, we considered sex differences only in medication prescription and were not able to determine whether those differences, where found, resulted in different levels of risk factor control and event rates. Furthermore, patients with established CVD seen in primary care may also receive treatment from secondary care. Also, it is not clear whether general practitioners or cardiologists would be the main source of prescriptions in any individual case. Finally, as the studies included in this review were conducted in mostly high-income countries, the generalizability of our findings to low- and middle-income countries needs to be assessed.

In conclusion, this meta-analysis, summarizing all recent literature, shows that sex differences in cardiovascular medication prescription persist in primary care. Future research is needed to determine the underlying causes of observed sex differences and to develop tailored strategies to optimize the use of evidence-based cardiovascular medication for both women and men.

ARTICLE INFORMATION

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Disclosures

Woodward is a consultant to Amgen and Kirin. The remaining authors have no disclosures to report.

Supplementary Materials

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Figures S1–S11
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Supplemental Material

Table S1. Search terms.

	Pubmed	EMBASE	Search names
Primary care	Primary Health Care [Mesh] Primary service [tiab] GP [tiab] Primary Health Care [tiab] Primary healthcare [tiab] Primary medical care [tiab] General practitioner [tiab] General practice [tiab] Family doctor [tiab] Family practitioner [tiab] Family physician [tiab]	(primary adj3 care*).tw. primary service*.tw. GP.tw. General practice*.tw. Primary health?care.tw. exp primary medical care/ exp general practitioner/ exp general practice/ (family adj (doctor or practitioner or physician)).tw.	Primary care v1 Primary care v2
CVD risk scores	Cardiovascular score [tiab] Cardiovascular risk score [tiab] ASSIGN score [tiab] Qrisk [tiab] Systematic Coronary Risk Evaluation [tiab] Framingham score [tiab] Framingham risk [tiab] Framingham index [tiab] Pooled cohort equation [tiab]	Exp cardiovascular risk/ (cardiovascular adj2 score).tw. (assign adj score).tw. QRisk.tw. Systematic Coronary Risk Evaluation.tw. (Framingham adj4 (score or risk or index)).tw. pooled cohort equation.tw.	Cvd risk scores v1 *risk factor will go in risk factor section.
Primary prevention	Primary prevention [MeSH] Primary prevention [tiab]	exp primary prevention/ (primary adj2 prevention).tw.	Primary prevention v1 Primary prevention v2
Secondary prevention	Secondary prevention [MeSH] Secondary prevention [tiab]	exp secondary prevention/ (secondary adj2 prevention).tw.	Secondary prevention v1 Secondary prevention v2

	Pubmed	EMBASE	Search names
Sex	Male[MeSH] Male[tiab] Men[tiab] Man[tiab] Female[MeSH] Female[tiab] Women[tiab] Woman[tiab] Sex[MeSH] Sex[tiab] Gender[tiab]	male/ (mean or man or male).tw. female/ (woman or women or female).tw. gender/ sex/ (gender* or sex*).tw.	Men and women v2 Sex gender v2
Risk assess	Risk factors[MeSH] Risk factors [tiab] Risk assessment [MeSH] Risk assessment [tiab] Absolute risk [tiab] Health screen [tiab] Health screening [tiab] Health measurement [tiab] Health assessment [tiab] Health care disparity [MeSH] Health care disparity [tiab] Health care disparities [tiab]	Exp risk factor/ Exp risk assessment/ (risk adj5 (assess* or measure* or screem*)).tw. (absolute adj5 risk*).tw. exp health care disparity/ (health? Care adj3 disparit*).tw.	Risk assess v2 Risk assess v4
Drugs	(statin* or lipid lowering).tw. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ ((blood pressure adj3 medication*) or	cardiovascular drugs/therapeutic use [Mesh] cardiovascular diseases/therapy [mesh] Hydroxymethylglutaryl-CoA Reductase Inhibitors [Mesh]	standalone: combined with drugs tab: all drug terns and meds v2 same as angiotensin II receptor

	Pubmed	EMBASE	Search names
	blood pressure lowering or bp?lowering).tw. exp antihypertensive agent/ (angiotensin II receptor blocker* or ARB*).tw. (angiotensin?converting enzyme inhibitor* or ACE* or ACEI* or ACEi*).tw. exp dipeptidyl carboxypeptidase inhibitor/ (beta blocker* or b?blocker*).tw. exp beta adrenergic receptor blocking agent/ antiplatelet.tw. exp antithrombocytic agent/ aspirin.tw antithrombotic*.tw exp nonsteroid antiinflammatory agent/ ((calcium?channel and (blocker* or blocking)) or (calcium adj2 antagonist*) or calcium?antagonist* or CCB*).tw. exp calcium channel blocking agent/ exp diuretic agent/ diuretic*.tw.	statin [tiab] statins [tiab] lipid lowering [tiab] blood pressure medication [tiab] blood pressure lowering [tiab] bp lowering [tiab] antihypertensive agent [Mesh] antihypertensive [tiab] Angiotensin Receptor Antagonists [Mesh] Angiotensin Receptor Antagonist [tiab] Angiotensin Receptor Antagonists [tiab] angiotensin II receptor blocker [tiab] angiotensin II receptor blockers [tiab] angiotensin 2 receptor blocker [tiab] angiotensin 2 receptor blockers [tiab] ARB[tiab] ARBs[tiab] Angiotensin Converting Enzyme Inhibitors [Mesh] Angiotensin Converting Enzyme Inhibitor [tiab] Angiotensin Converting Enzyme Inhibitors [tiab] ACE inhibitor [tiab] ACE inhibitors [tiab] ACEi [tiab] Adrenergic beta-Antagonists [Mesh]	blocker [mesh] CVD meds v2

	Pubmed	EMBASE	Search names
		beta blocker [tiab] beta blockers [tiab] b blocker [tiab] b blockers [tiab] Anti-Inflammatory Agents, Non-Steroidal [Mesh] antithrombotic [tiab] antithrombotics [tiab] antiplatelet [tiab] aspirin [MeSH] aspirin [tiab] Calcium Channel Blockers [MeSH] Calcium Channel Blocker [tiab] Calcium Channel Blockers [tiab] calcium antagonist [tiab] calcium antagonists [tiab] CCB [tiab] CCBs [tiab] diuretics [Mesh] diuretic [tiab] diuretics [tiab]	

Table S2. Data extraction form.

Study (author)		
Publication year		
Source	Study ID (Corresponding with reference software)	
	Reviewer ID (MZ, EM, or KH)	
Study design	Study type	
Study characteristics	Year of study	
	Performed country	
Patient characteristics	CVD status	
	Prevention type	
	Age	
	Women	
	Mean women	
	Men	
	Mean men	
Aspirin	Study sample	
	Study women	
	Number of women on medications	
	Percentage of women on medications	
	Number of men on medications	
	Percentage of women on medications	
	Differences (women-men)	
	Women-to-men prevalence ratio	
	Maximum adjustment available	
Statins	Study sample	
	Study women	
	Number of women on medications	
	Percentage of women on medications	
	Number of men on medications	
	Percentage of women on medications	
	Differences (women-men)	
	Women-to-men prevalence ratio	
	Maximum adjustment available	
Beta blockers	Study sample	
	Study women	
	Number of women on medications	
	Percentage of women on medications	
	Number of men on medications	
	Percentage of women on medications	

Study (author)		
	Differences (women-men)	
	Women-to-men prevalence ratio	
	Maximum adjustment available	
Calcium channel blockers	Study sample	
	Study women	
	Number of women on medications	
	Percentage of women on medications	
	Number of men on medications	
	Percentage of women on medications	
	Differences (women-men)	
	Women-to-men prevalence ratio	
	Maximum adjustment available	
ACE-inhibitors	Study sample	
	Study women	
	Number of women on medications	
	Percentage of women on medications	
	Number of men on medications	
	Percentage of women on medications	
	Differences (women-men)	
	Women-to-men prevalence ratio	
	Maximum adjustment available	
Diuretics	Study sample	
	Study women	
	Number of women on medications	
	Percentage of women on medications	
	Number of men on medications	
	Percentage of women on medications	
	Differences (women-men)	
	Women-to-men prevalence ratio	
	Maximum adjustment available	
Key findings		

Table S3. Quality assessment tool: Newcastle-Ottawa Scale.

Selection: (Maximum 3 stars)

1) Representativeness of the sample:

a) Truly representative of the average in the target population. * (all subjects or random sampling)

b) Somewhat representative of the average in the target population. * (non-random sampling)

c) Selected group of users.

d) No description of the sampling strategy.

2) Sample size:

a) Justified and satisfactory. *

b) Not justified.

3) Non-respondents:

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.

c) No description of the response rate or the characteristics of the responders and the non-responders.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study controls for the most important factor (age). *

b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

a) Independent blind assessment. **

b) Record linkage. **

c) Self report. *

d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incomplete.

Studies with more than four stars will be counted as satisfactory and thus can be included in systematic review.

Table S4. Quality assessment.

Study		Selection (3)			Comparability (2)	Outcome(3)		Total
Study	Year	Representativeness	Sample size	Non-respondent	Adjustment	Outcome	Statistical test	
Carlsson A.C. et al[21]	2012	1	1	1	1	2	1	7
Carroll K et al[22]	2003	1	1	1	1	2	1	7
Catalan-Ramos A et al[32]	2014	1	1	1	0	2	1	6
Al-Lawati J.A. et al[10]	2012	1	1	1	0	2	1	6
Crilly M et al[23]	2007	1	1	1	2	2	1	8
Dodhia H et al[33]	2015	1	1	1	2	2	1	8
Dreyer R et al[34]	2009	1	1	1	2	2	1	8
Driscoll A. et al[24]	2011	1	1	1	2	2	1	8
Emberson J.R. et al[25]	2005	1	1	1	2	2	1	8
Forster A.S. et al[35]	2014	1	1	1	0	2	1	6
Greving J.P. et al[49]	2004	1	1	1	2	2	1	8
Gulliford M.C. et al[36]	2010	1	1	1	2	2	1	8
Hawkins N.M. et al[50]	2012	1	1	1	2	2	1	8
Hendrix K.H. et al[26]	2005	1	1	1	0	2	0	5
Hippisley-Cox J et al[27]	2001	1	1	1	2	2	1	8
Hyun K. et al[37]	2012	1	1	1	2	2	1	8
Journath G. et al[38]	2008	1	1	1	1	2	1	7
Brady A.J.B. et al[20]	2005	1	1	1	0	2	0	5
Weler D.J. et al[18]	2005	1	1	1	2	2	1	8
Paulsen M.S. et al[48]	2011	1	1	1	2	2	1	8
Lahoz C. et al[12]	2009	1	1	1	2	2	1	8

Study		Selection (3)			Comparability (2)	Outcome(3)		Total
Study	Year	Representativeness	Sample size	Non-respondent	Adjustment	Outcome	Statistical test	
Sheppard J.P. et al[41]	2014	1	1	1	0	2	0	5
Svilaas A et al[16]	2000	1	1	1	0	2	1	6
Tabenkin H et al[17]	2010	1	1	1	2	2	1	8
Turnbull F et al[42]	2010	1	1	1	1	1	1	6
Virani S.S. et al[43]	2011	1	1	1	2	2	1	8
Majeed A. et al[39]	2000	1	1	1	0	2	0	5
Majeed A. et al[14]	2005	1	1	1	0	2	0	5
Murphy N. et al[51]	2004	1	1	1	2	2	1	8
Nilsson P.M. et al[52]	2007	1	1	1	0	2	1	6
Nilsson P.M. et al[40]	2004	1	1	1	1	2	1	7
Owen A. et al[47]	2009	1	1	1	2	0	1	6
Lawlor D.A. et al[29]	2004	1	1	1	2	2	1	8
Bull N et al[31]	2003	1	1	1	2	2	1	8
Macchia A et al[13]	2012	1	1	1	2	2	1	8
Qato D.M et al[15]	2016	1	1	1	2	1	1	7
Saposnik G. et al[30]	2009	1	1	1	0	1	1	5
Brady A.J. et al[20]	2001	1	1	1	0	2	0	5
Alberts M.J. et al[28]	2009	1	1	1	0	2	1	6
Lee C. et al[19]	2019	1	1	1	2	2	1	8
Wandell P. et al[45]	2018	1	1	1	1	2	1	7
Law T.K. et al[44]	2015	1	1	1	0	1	1	5

Table S5. Sex difference on aspirin prescription.

Study, year	CVD status	Age	Age of women	Age of men	% for women	% for men	Unadjusted PR	Adjusted PR¶
Brady, 1998[11]	CVD	67	NA	NA	46%	53%	0.86 (0.83-0.88)	0.88 (0.81-0.95)
Macchia, 2005[13]	CVD	NA	NA	NA	78%	85%	0.92 (0.91-0.93)	NA
Qato D.M, 2011[15]	Mixed (CVD+High-risk**)	52	NA	NA	60%	63%	0.96 (0.91-1.01)	0.84 (0.71-0.98)
Al-Lawati, 2012*[10]	Mixed (CVD+DM)	54	54	54	67%	67%	1.00 (0.95-1.06)	0.85 (0.74-0.97)
Brady, 2002[20]	CVD	67	NA	NA	74%	80%	0.92 (0.90-0.94)	0.88 (0.81-0.95)
Carlsson, 2002[21]	CVD	76	75	74	35%	32%	1.09 (1.02-1.16)	0.91 (0.79-1.04)
Carroll, 2001[22]	CVD	NA	NA	NA	59%	65%	0.90 (0.87-0.94)	NA
Crilly, 2001[23]	CVD	69	NA	NA	81%	86%	0.94 (0.89-0.99)	0.89 (0.81-0.97)
Driscoll, 2007[24]	CVD	73	74	72	71%	80%	0.89 (0.87-0.91)	0.90 (0.80-1.01)
Emberson, 2001[25]	Mixed (CVD+DM)	NA	NA	NA	14%	27%	0.51 (0.47-0.56)	NA
Hendrix, 2005*[26]	Mixed (CVD+HTN)	NA	NA	NA	15%	39%	0.38 (0.37-0.39)	NA
Hippisley-Cox, 2001*[27]	Mixed, (CVD+High-risk**)	NA	NA	NA	71%	76%	0.94 (0.91-0.97)	NA
Weler, 2003[18]	Mixed (CVD+DM)	65	66	63	46%	57%	0.80 (0.75-0.85)	0.88 (0.81-0.94)
Lahoz, 2008*[12]	CVD	65	NA	NA	55%	64%	0.87 (0.83-0.90)	0.88 (0.82-0.94)
Majeed, 2002[14]	CVD	NA	NA	NA	59%	66%	0.89 (0.83-0.95)	NA
Svilaas, 1997[16]	CVD	69	NA	NA	47%	58%	0.81 (0.74-0.89)	0.89 (0.82-0.97)
Tabenkin, 2004[17]	Mixed (CVD+HTN)	53	52	53	35%	55%	0.64 (0.51-0.80)	0.84 (0.73-0.98)
Lee, 2018[19]	CVD	67	65	68	41%	57%	0.72 (0.71, 0.73)	0.88 (0.81, 0.95)
Pooled		64	67	65	41%	56%	0.81 (0.73-0.92)	0.87 (0.81-0.94)

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; mixed: patients at high-risks and with established cardiovascular disease; DM: diabetes; HTN: hypertension

*Publication year

** No high-risk assessment tool is available

¶ Mean age of study population in each study was adjusted.

Table S6. Sex difference on statin prescription.

Study, year	CVD status	Age	Age of Women	Age of men	% for women	% for men	Unadjusted PR	Adjusted PR ¶
Alberts, 2004[28]	CVD	69	NA	NA	66%	69%	0.96 (0.94-0.97)	0.87 (0.82-0.92)
Brady, 1998[11]	CVD	69	NA	NA	13%	18%	0.73 (0.69-0.78)	0.87 (0.82-0.92)
Lawlor, 2000[29]	CVD	60-79	NA	NA	27%	24%	1.12 (0.93-1.36)	NA
Macchia, 2005[13]	CVD	68.1	74	65	67%	80%	0.84 (0.83-0.86)	0.88 (0.83-0.93)
Qato, 2011[15]	High-risk**	52.2	NA	NA	25%	25%	1.00 (0.90-1.11)	1.05 (0.94-1.18)
Saposnik, 2004[30]	CVD	67	NA	NA	79%	78%	1.01 (0.95-1.08)	0.89 (0.84-0.93)
Brady, 2002[20]	CVD	67	NA	NA	45%	52%	0.87 (0.83-0.90)	0.89 (0.84-0.93)
Bull, 2003[31]	CVD	>40	NA	NA	21%	28%	0.75 (0.70-0.79)	NA
Carlsson, 2002[21]	CVD	75.5	75	74	18%	24%	0.78 (0.71-0.85)	0.81 (0.73-0.89)
Carroll K, 2001[22]	CVD	>44	NA	NA	38%	49%	0.77 (0.73-0.82)	NA
Catalan-Ramos, 2009[32]	High-risk, defined by FRS	51	NA	NA	71%	70%	1.01 (1.00-1.02)	1.07 (0.94, 1.20)
Crilly, 2001[23]	CVD	69	71	67	53%	56%	0.93 (0.84-1.04)	0.87 (0.82-0.92)
Dodhia, 2013[33]	CVD	70	NA	NA	75%	83%	0.90 (1.03-1.09)	0.86 (0.81-0.91)
Dreyer, 2007[34]	CVD	70	NA	NA	76%	85%	0.89 (0.85-0.94)	0.86 (0.81-0.91)
Emberson, 2001[25]	Mixed (CVD+DM)	60-79	NA	NA	8%	7%	1.10 (0.95-1.29)	NA
Forster, 2013[35]	High-risk, NHS health check	40-74	NA	NA	21%	18%	1.21 (1.14-1.29)	NA
Gulliford, 2010[36]	CVD	73	NA	NA	16%	19%	0.85 (0.79-0.92)	0.83 (0.77-0.90)
Hendrix, 2005*[26]	Mixed (CVD+HTN)	62	NA	NA	29%	41%	0.70 (0.69-0.72)	0.94 (0.89-1.00)
Hyun, 2012[37]	Mixed (CVD+high risk defined by FRS)	61	NA	NA	66%	68%	0.97 (0.95-0.99)	0.95 (0.90-1.01)

Study, year	CVD status	Age	Age of Women	Age of men	% for women	% for men	Unadjusted PR	Adjusted PR ¶
Journath, 2005[38]	High-risk (HTN)	66	67	65	28%	33%	0.85 (0.79-0.92)	0.90 (0.85-0.94)
Lahoz, 2008*[12]	CVD	65	68	65	77%	80%	0.96 (0.93-0.98)	0.91 (0.86-0.95)
Majeed, 1996[39]	CVD	NA	NA	NA	8%	13%	0.62 (0.59-0.65)	NA
Nilsson, 2009[52]	Mixed (CVD+HTN))	65	NA	NA	96%	92%	1.04 (1.03-1.05)	0.91 (0.86-0.95)
Sheppard, 2009[41]	Mixed (CVD+High-risk defined by FRS)	54	NA	NA	92%	72%	1.27 (1.24-1.31)	1.03 (0.93-1.14)
Turnbull, 2008[42]	Mixed (CVD+ high-risk defined by FRS)	68	68	68	53%	59%	0.90 (0.85-0.95)	0.88 (0.83-0.93)
Virani, 2011[43]	CVD	71	66	71	58%	65%	0.89 (0.88-0.90)	0.85 (0.79-0.91)
Law, 2010[44]	High-risk, defined by FRS	58	NA	NA	91%	93%	0.97 (0.91-1.04)	0.98 (0.91-1.06)
Lee, 2018[19]	CVD	67	65	68	56%	75%	0.74 (0.73, 0.74)	0.89 (0.84, 0.93)
Wandell, 2007[45]	CVD	NA	NA	NA	33%	39%	0.84 (0.79, 0.89)	NA
Nanna, 2015[46]	Mixed (CVD+High-risk**)	68	68	68	67%	78%	0.85 (0.83, 0.88)	0.88 (0.83-0.93)
Pooled		65	71	68	60%	63%	0.90 (0.85, 0.95)	0.91 (0.87-0.95)

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; mixed: patients at high-risks and with established CVD; FRS: Framingham risk score; HTN: hypertension; DM: diabetes

*Publication year

**No cardiovascular risk assessment tool is available

¶ Mean age of study population in each study was adjusted.

Table S7. Sex difference on beta-blockers prescription.

Study, year	CVD status	Age	Age of women	Age of men	% for women	% for men	Unadjusted PR	Adjusted PR ¶
Brady, 1998[11]	CVD	69	NA	NA	19%	23%	0.86 (0.81-0.90)	0.91 (0.85-0.97)
Macchia, 2003[13]	CVD	68	74	65	64%	68%	0.93 (0.91-0.95)	0.92 (0.86-0.97)
Al-Lawati, 2007[10]	Mixed (CVD+DM)	54	54	54	7%	7%	1.08 (0.73-1.59)	1.00 (0.88-1.14)
Brady, 2002[20]	CVD	67	NA	NA	38%	42%	0.91 (0.87-0.95)	0.92 (0.87-0.98)
Carlsson, 2013[21]	CVD	76	75	74	59%	55%	1.07 (1.03-1.11)	0.87 (0.77-0.98)
Carroll, 2001[22]	CVD	>44	NA	NA	20%	22%	0.91 (1.09-1.10)	NA
Catalan-Ramos, 2009[32]	High-risks, defined by FRS	51	NA	NA	40%	36%	1.09 (1.08-1.10)	1.02 (0.87-1.19)
Crilly M, 2001[23]	CVD	69	71	67	28%	38%	0.74 (0.63-0.88)	0.91 (0.85-0.97)
Dreyer, 2001[34]	CVD	70	NA	NA	51%	55%	0.93 (0.85-1.01)	0.90 (0.84-0.97)
Emberson, 2001[25]	Mixed (CVD+DM)	60-79	NA	NA	25%	17%	1.49 (1.37-1.62)	NA
Greving, 2000[49]	High-risks (HTN)	63	NA	NA	41%	41%	1.01 (0.95-1.07)	0.94 (0.89-1.00)
Hawkins,2007[50]	CVD	68	NA	NA	24%	28%	0.86 (0.82-0.89)	0.92 (0.86-0.97)
Hendrix, 2005*[26]	Mixed (CVD+HTN)	62	NA	NA	28%	32%	0.86 (0.84-0.88)	0.95 (0.89-1.01)
Hippisley-Cox, 2001*[27]	CVD	62	NA	NA	49%	51%	0.96 (0.91=1.01)	0.95 (0.89-1.01)
Journath, 2005[38]	High-risks (HTN)	66	67	65	54%	51%	1.05 (1.01-1.11)	0.93 (0.88-0.98)
Lahoz, 2008*[12]	CVD	65	68	65	41%	49%	0.83 (0.78-0.87)	0.93 (0.88-0.99)
Murphy,2004[51]	High-risks (HTN)	NA	NA	NA	20%	23%	0.86 (0.68-1.09)	NA
Owen, 2009[47]	High-risks (DM)	63	63	62	19%	19%	0.99 (0.92-1.06)	0.94 (0.89-1.00)
Paulsen, 2011[48]	High-risks (HTN)	66	66	66	29%	28%	1.04 (0.96-1.13)	0.98 (0.90-1.06)
Lee, 2018[19]	CVD	67	65	68	38%	50%	0.76 (0.75,0.77)	0.93 (0.88, 0.98)
Wandell, 2007[45]	CVD	NA	NA	NA	79%	75%	1.05 (1.02, 1.07)	NA
Pooled		65	69	66	38%	38%	0.95 (0.89, 1.02)	0.93 (0.88, 0.99)

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; DM: diabetes; FRS: Framingham risk score; HTN: hypertension

*Publication year

¶ Mean age of study population in each study was adjusted.

Table S8. Sex difference on calcium channel blockers prescription.

Study, year	CVD status	Age	Age of women	Age of men	% for women	% for men	Unadjusted PR	Adjusted PR ¶
Brady, 1998[11]	CVD	69	NA	NA	12%	14%	0.85 (0.80-0.91)	0.98 (0.87-1.13)
Al-Lawati, 2007[10]	High-risks (DM)	54	54	54	2%	1%	1.38 (0.58-3.27)	0.87 (0.72-1.04)
Carlsson, 2013[21]	CVD	75	75	74	7%	6%	1.17 (0.97-1.40)	1.04 (0.85-1.29)
Catalan-Ramos, 2009[32]	High-risks (HTN)	51	NA	NA	25%	27%	0.94 (0.93-0.95)	0.85 (0.67-1.05)
Dreyer, 2007[34]	CVD	70	NA	NA	39%	31%	1.26 (1.11-1.42)	1.00 (0.86-1.16)
Greving, 2000[49]	High-risks (HTN)	63	NA	NA	18%	24%	0.74 (0.68-0.81)	0.94 (0.85-1.04)
Hendrix, 2005*[26]	Mixed (CVD+HTN)	62	NA	NA	30%	28%	1.08 (1.05-1.10)	0.93 (0.84-1.03)
Journath, 2005[38]	High-risks (HTN)	66	67	65	26%	34%	0.78 (0.72-0.84)	0.96 (0.86-1.07)
Lahoz, 2008*[12]	CVD	65	68	65	27%	24%	1.13 (1.04-1.23)	1.18 (1.06-1.31)
Nilsson, 2007*[52]	High-risks (HTN)	52	53	51	26%	34%	0.77 (0.64-0.92)	0.68 (0.53-0.89)
Owen, 2009[47]	High-risks (DM+HTN)	63	63	62	26%	27%	0.96 (0.90-1.02)	0.94 (0.87-1.02)
Paulsen, 2011[48]	High-risks (HTN)	66	66	66	32%	38%	0.84 (0.78-0.90)	0.61 (0.55-0.69)
Wandell, 2007[45]	CVD	NA	NA	NA	37%	34%	1.07 (1.01, 1.14)	NA
Pooled		63	65	64	25%	26%	0.95 (0.87-1.05)	0.94 (0.85-1.04)

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; HTN: hypertension; DM: diabetes

*Publication year

¶ Mean age of study population in each study was adjusted.

Table S9. Sex difference on ACE-inhibitors prescription.

Author, year	CVD status	Age	Age of women	Age of men	% for women	% for men	Unadjusted PR	Adjusted PR ¶
Brady , 1998[11]	CVD	69	NA	NA	12%	14%	0.85 (0.80-0.91)	0.84 (0.79-0.89)
Macchina, 2011[13]	CVD	68	74	65	79%	79%	1.00 (0.98-1.01)	0.81 (0.66-0.99)
Al-Lawati, 2007[10]	High-risks (DM)	54	54	54	37%	46%	0.80 (0.71-0.92)	0.74 (0.57-0.96)
Brady, 2002[20]	CVD	67	NA	NA	25%	28%	0.89 (0.84-0.95)	0.81 (0.67-0.97)
Catalan-Ramos, 2009[32]	High-risks (HTN)	51	NA	NA	53%	59%	0.90 (0.89, 0.90)	0.73 (0.52-1.01)
Dreyer, 2007[34]	CVD	70	NA	NA	44%	52%	0.85 (0.77-0.93)	0.82 (0.65-1.05)
Emberson, 2001[25]	Mixed (CVD+DM)	60-79	NA	NA	26%	23%	1.11 (1.03-1.20)	NA
Greving, 2000[49]	High-risks (HTN)	63	NA	NA	28%	37%	0.76 (0.71-0.82)	0.78 (0.67-0.91)
Hawkins, 2007[50]	CVD	68	NA	NA	52%	56%	0.92 (0.90-0.94)	0.81 (0.66-0.99)
Hendrix, 2005*[26]	Mixed (CVD+HTN)	62	NA	NA	44%	52%	0.85 (0.84-0.87)	0.78 (0.67-0.91)
Journath, 2005[38]	High-risks (HTN)	66	67	65	18%	27%	0.67 (0.61-0.73)	0.80 (0.67-0.95)
Lahoz, 2008*[12]	CVD	65	68	65	40%	39%	1.01 (0.95-1.07)	0.80 (0.68-0.94)
Majeed, 2002[14]	CVD	NA	NA	NA	68%	76%	0.89 (0.85-0.94)	NA
Murphy, 2004[51]	CVD	NA	NA	NA	34%	46%	0.74 (0.64-0.87)	NA
Nilsson, 2007*[52]	High-risks (HTN)	52	53	51	18%	27%	0.67 (0.53-0.83)	0.73 (0.54-0.99)
Nilsson, 2004[40]	Mixed (CVD+DM)	65	NA	NA	27%	33%	0.80 (0.76-0.86)	0.80 (0.68-0.94)
Owen, 2009[47]	High-risks (DM+HTN)	62	63	62	45%	51%	0.87 (0.84-0.91)	0.78 (0.67-0.91)
Paulsen, 2011[48]	High-risks (HTN)	66	66	66	37%	48%	0.77 (0.72-0.82)	0.80 (0.67-0.95)
Tabenkin, 2004[17]	High-risks (HTN)	53	52	53	41%	52%	0.79 (0.64-0.98)	0.73 (0.55-0.98)
Lee, 2018[19]	CVD	67	65	68	55%	69%	0.80 (0.80, 0.81)	0.80 (0.68, 0.95)
Wandell, 2007[45]	CVD	NA	NA	NA	33%	40%	0.83 (0.78, 0.88)	NA
Pooled		63	65	61	51%	57%	0.85 (0.81, 0.89)	0.84 (0.79, 0.89)

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; mixed: patients at high-risks and with established CVD; DM: diabetes; HTN: hypertension

*Publication year

¶ Mean age of study population in each study was adjusted.

Table S10. Sex difference on diuretics prescription.

Author, year	CVD status	Age	Age of women	Age of men	% for women	% for men	Unadjusted PR	Adjusted PR ¶
Brady, 1998[11]	CVD	69	NA	NA	29%	19%	1.51 (1.42-1.61)	1.32 (1.20-1.44)
Al-Lawati, 2012[10]	High-risks (DM)	54	54	54	4%	4%	1.16 (0.68-2.01)	1.33 (1.17-1.53)
Carlsson, 2013[21]	CVD	76	76	75	56%	42%	1.33 (1.27-1.40)	1.30 (1.10-1.55)
Catalan-Ramos, 2009[32]	High-risks (HTN)	51	NA	NA	68%	48%	1.43 (1.42-1.44)	1.34 (1.14-1.58)
Greving, 2009[49]	High-risks (HTN)	63	NA	NA	47%	32%	1.48 (1.39, 1.58)	1.32 (1.22-1.43)
Hendrix, 2005*[26]	Mixed (CVD+HTN)	62	NA	NA	58%	50%	1.14 (1.13-1.16)	1.32 (1.22-1.44)
Journath, 2005[38]	High-risks (HTN)	66	67	65	64%	48%	1.35 (1.29-1.41)	1.32 (1.21-1.44)
Lahoz, 2008*[12]	CVD	65	68	65	46%	32%	1.43 (1.35-1.52)	1.31 (1.21-1.43)
Majeed, 2002[14]	CVD	NA	NA	NA	81%	79%	1.02 (0.98-1.07)	NA
Murphy, 2004[51]	CVD	NA	NA	NA	81%	80%	1.01 (0.95-1.07)	NA
Nilsson, 2007*[52]	High-risks (HTN)	52	53	51	59%	45%	1.31 (1.16-1.48)	1.37 (1.15-1.56)
Owen, 2009[47]	High-risks (DM+HTN)	63	63	62	23%	17%	1.34 (1.25-1.44)	1.32 (1.22-1.43)
Paulsen, 2011[48]	High-risks (HTN)	66	66	66	66%	57%	1.01 (0.97-1.05)	1.32 (1.20-1.44)
Wandell, 2007[45]	CVD	NA	NA	NA	69%	54%	1.28 (1.23, 1.32)	NA
Pooled		63	65	64	47%	39%	1.26 (1.17, 1.37)	1.32 (1.22-1.43)

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; Mixed: patients at high-risks and with established CVD; HTN: hypertension; DM: diabetes

*Publication year

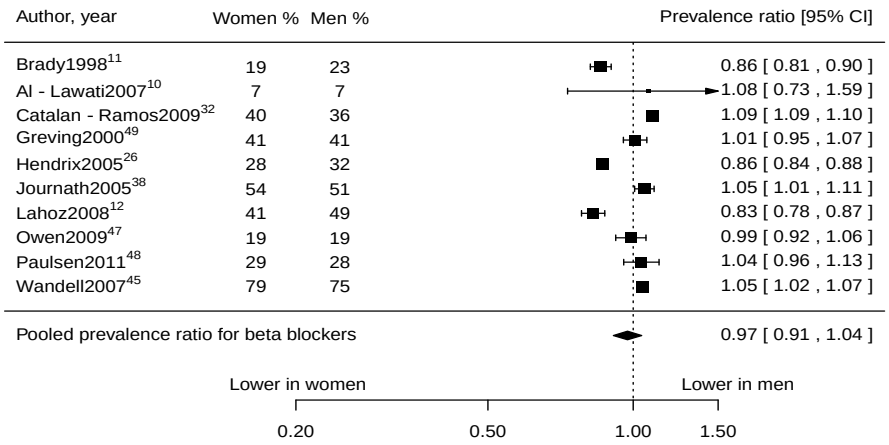
¶ Mean age of study population in each study was adjusted.

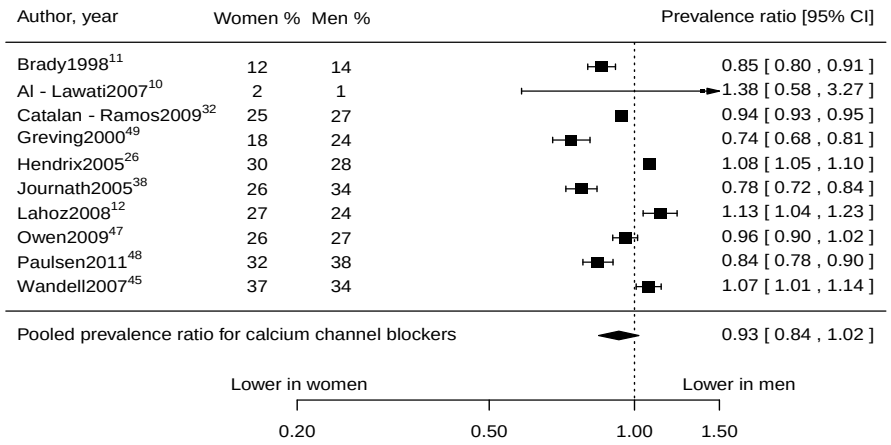
Table S11. Inclusion information, stratified by CVD status.

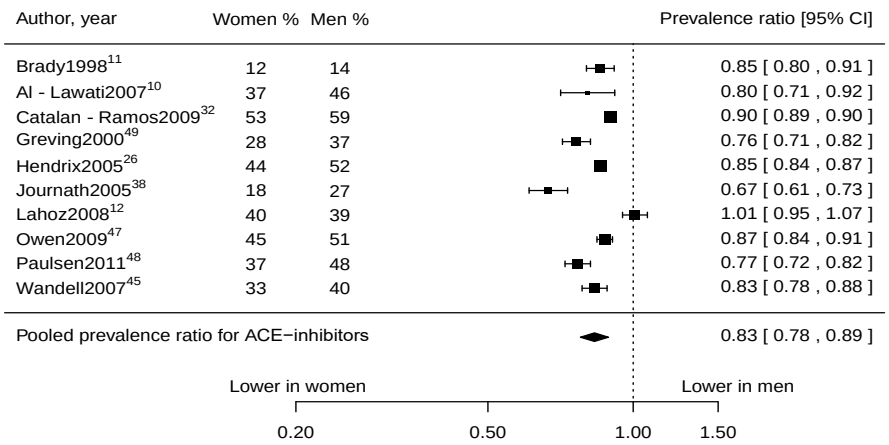
		Aspirin	Statin	BB	CCB	ACE-Inhibitor	Diuretics
High-risk	No. Paper	NA	7	7	7	8	7
	No. Women	NA	399,002	343,724	343,866	344,046	343,866
	No. Men	NA	406,962	344,523	344,504	344,726	344,204
	PP. women	NA	67%	39%	25%	52%	70%
	PP. men	NA	64%	36%	27%	58%	47%
	Pooled PR	NA	0.93(0.82,1.07)	1.04(0.96,1.12)	0.85(0.61,1.18)	0.79(0.49,1.26)	1.31(0.77,2.20)
CVD	No. Paper	11	19	12	5	10	6
	No. Women	98,294	170,702	111,640	19,733	104,151	15,364
	No. Men	130,704	1,177,332	140,974	30,903	130,772	24,027
	PP. women	48%	44%	38%	18%	50%	52%
	PP. men	62%	63%	47%	19%	58%	36%
	Pooled PR	0.89(0.84,0.94)	0.85(0.80,0.90)	0.90(0.85,0.96)	1.08(0.94,1.23)	0.88(0.84,0.93)	1.25(1.09,1.43)
Mixed	No. Paper	7	5	2	NA	3	NA
	No. Women	42,025	18,552	33,494	NA	37,787	NA
	No. Men	55,855	21,018	47,552	NA	52,634	NA
	PP. women	24%	61%	28%	NA	40%	NA
	PP. men	42%	61%	31%	NA	47%	NA
	Pooled PR	0.71(0.54,0.93)	1.05(0.93,1.18)	1.13(0.66,1.94)	NA	0.91(0.75,1.10)	NA

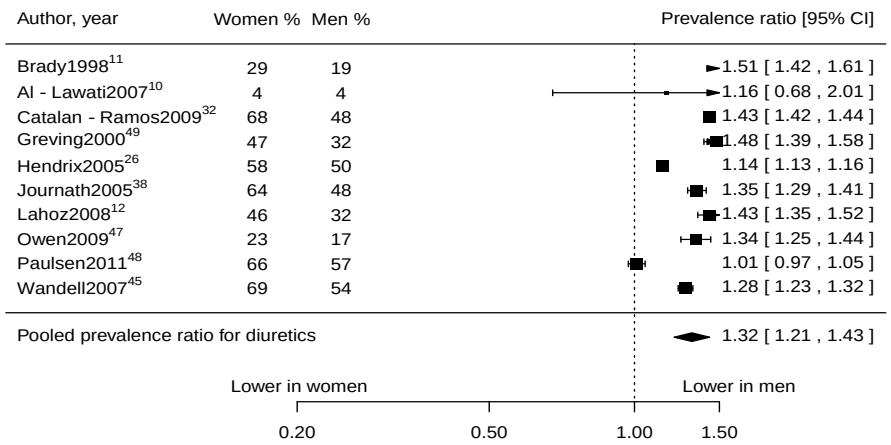
PP: Pooled prevalence; PR: prevalence ratio; CCB: calcium channel blocker; NA: not available

Figure S1. Women-to-men prevalence ratio from 10 studies reporting all four antihypertensive medications.



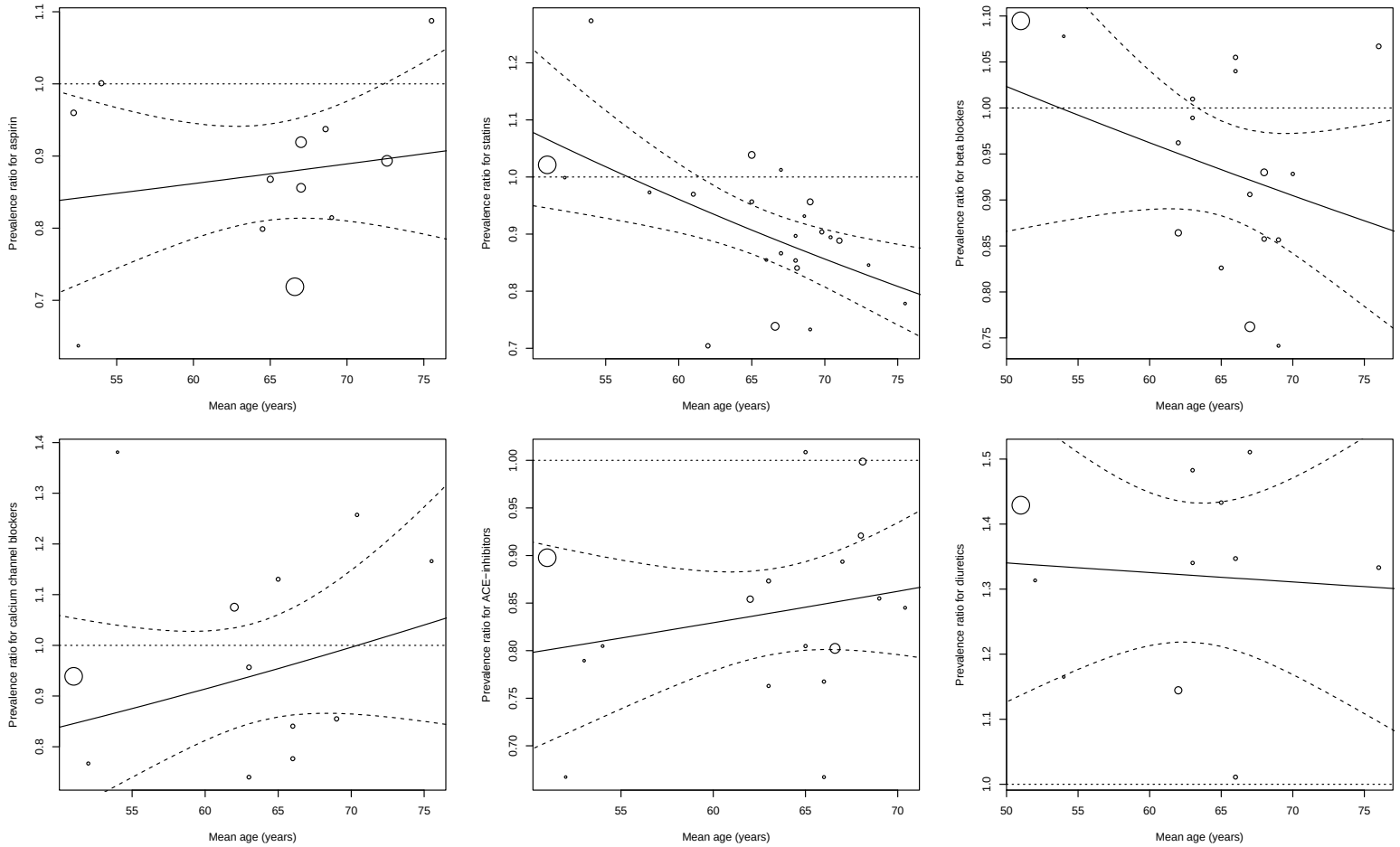






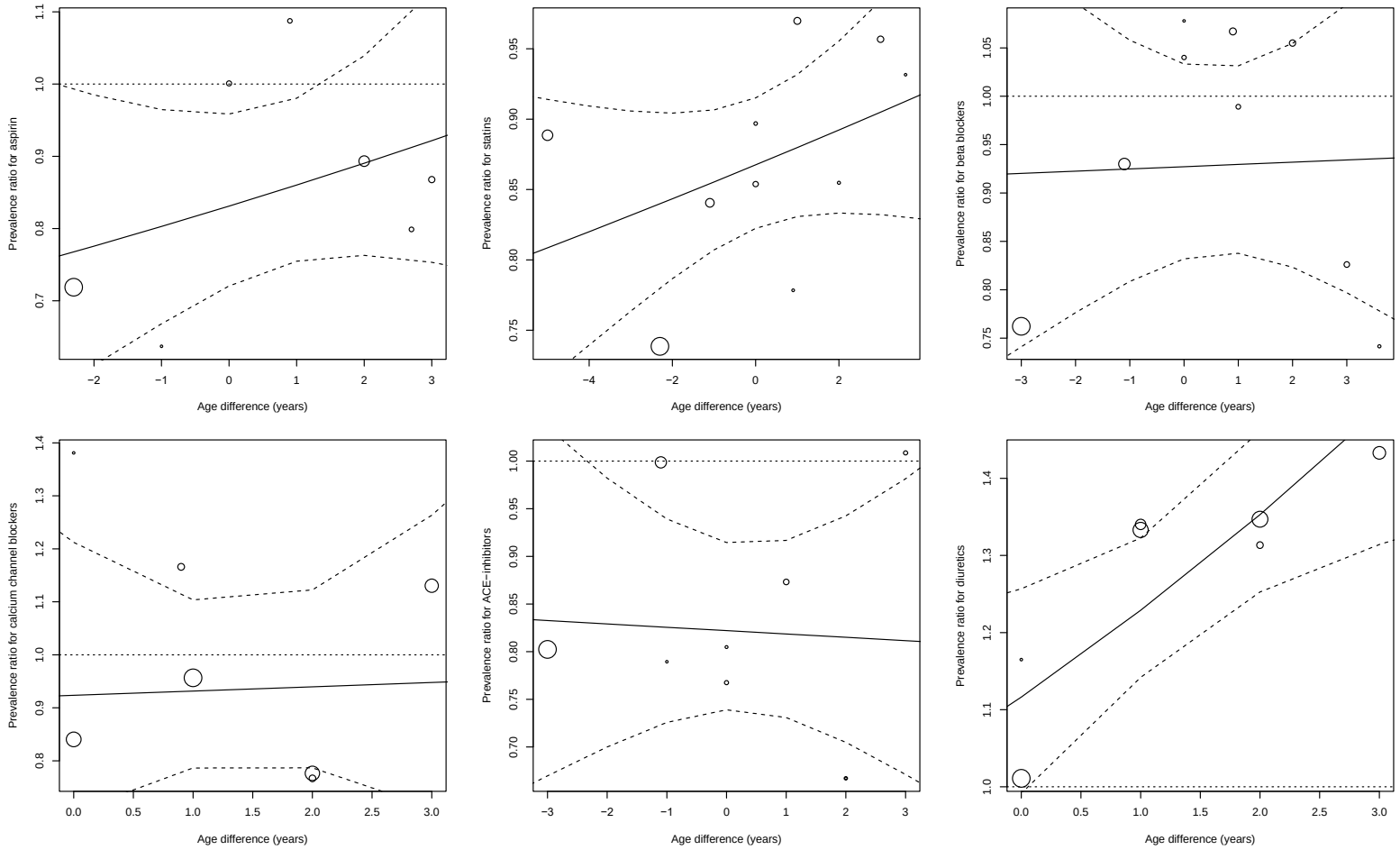
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.

Figure S2. Association between age and sex differences in the prescription of cardiovascular medication.



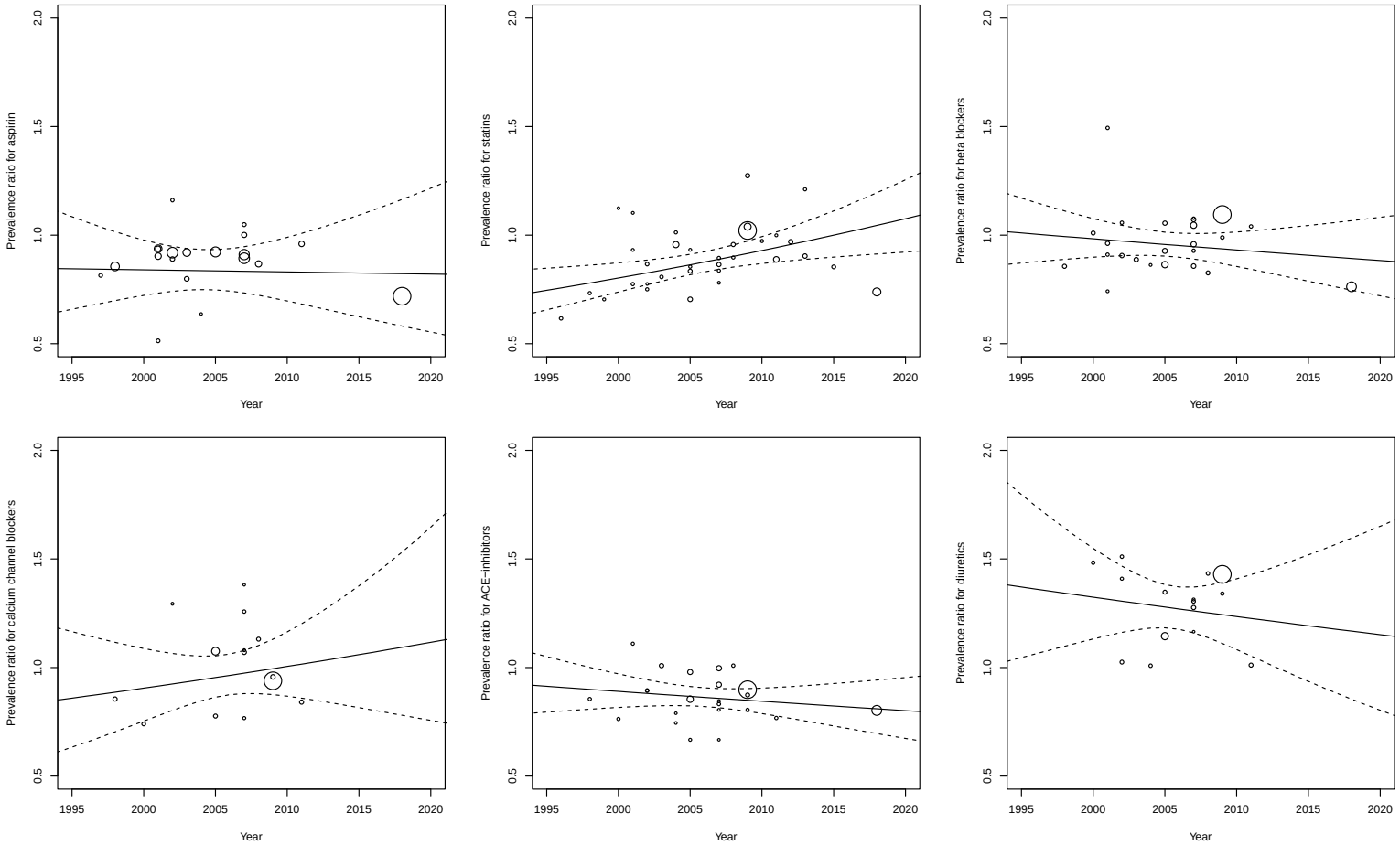
Bubbles are individual studies; diameters of the bubbles are proportional to studies weight for analysis.

Figure S3. Association between age difference between the sexes and sex differences in the prescription of cardiovascular medication.



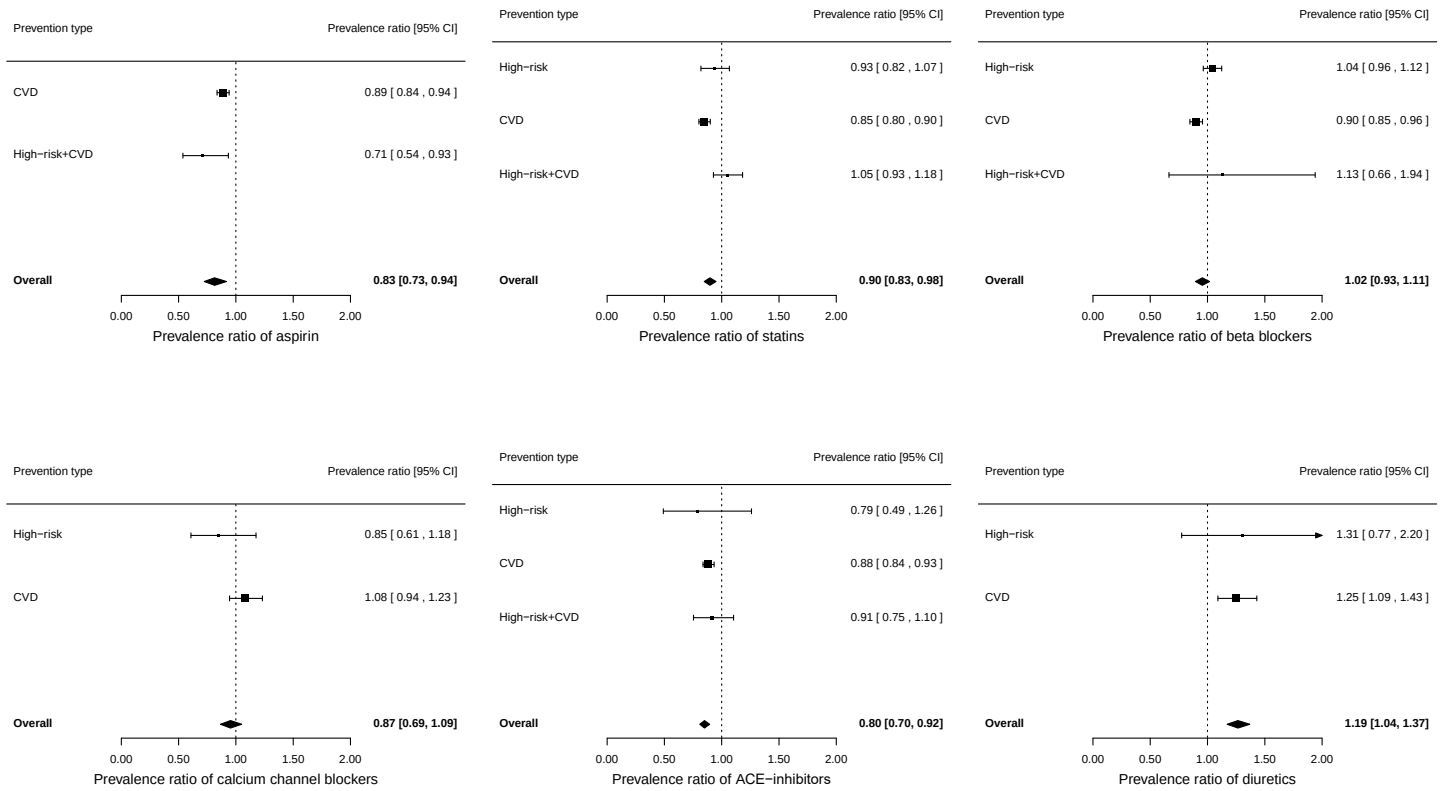
Bubbles are individual studies; diameters of the bubbles are proportional to studies weight for analysis.

Figure S4. Yearly trend of sex differences in the prescription of cardiovascular medication.



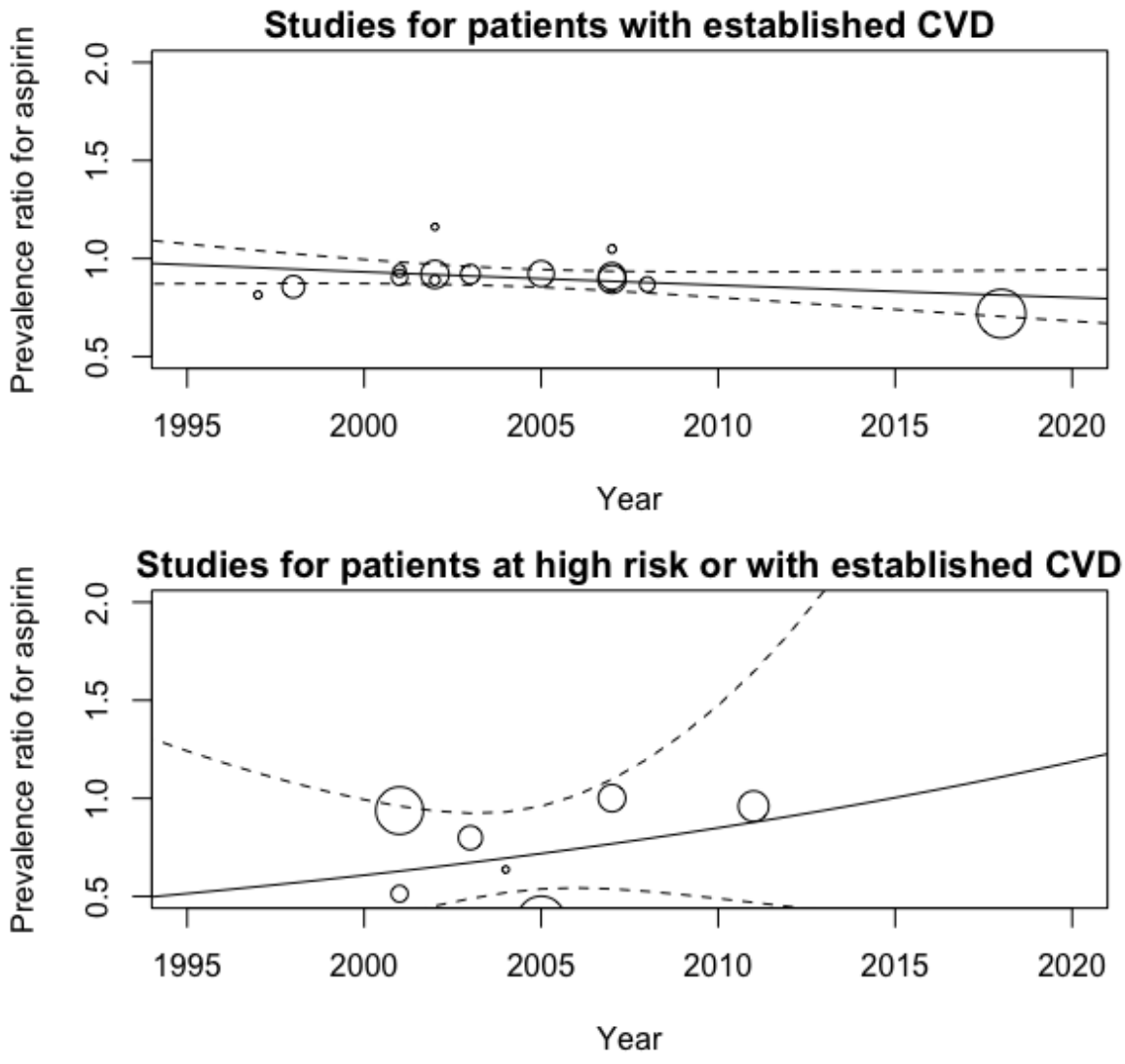
Bubbles are individual studies; diameters of the bubbles are proportional to studies weight for analysis.

Figure S5. Women-to-men prevalence ratio of cardiovascular medication prescription, stratified by CVD status.



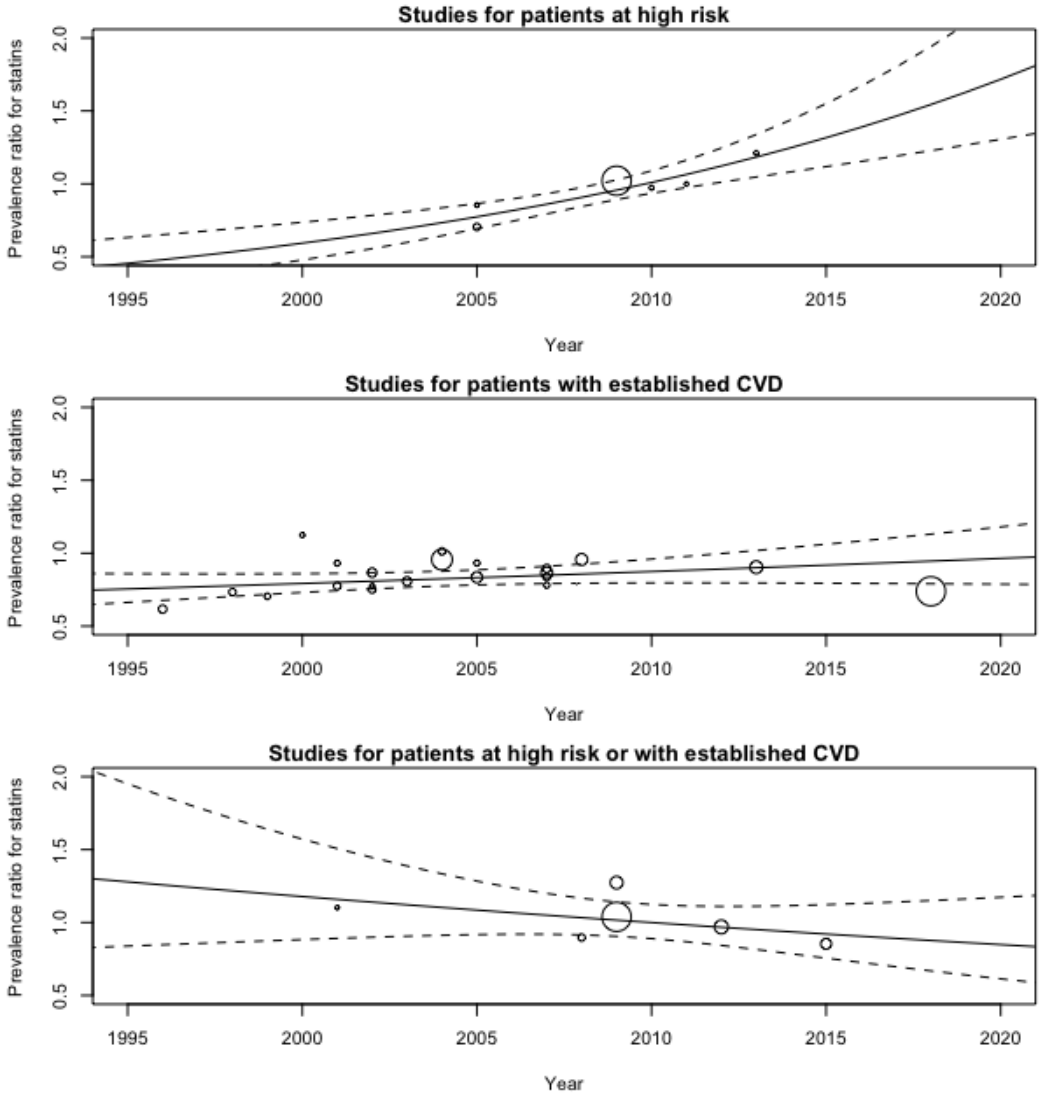
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.

Figure S6. Women-to-men prevalence ratio of aspirin prescription, stratified by CVD status.



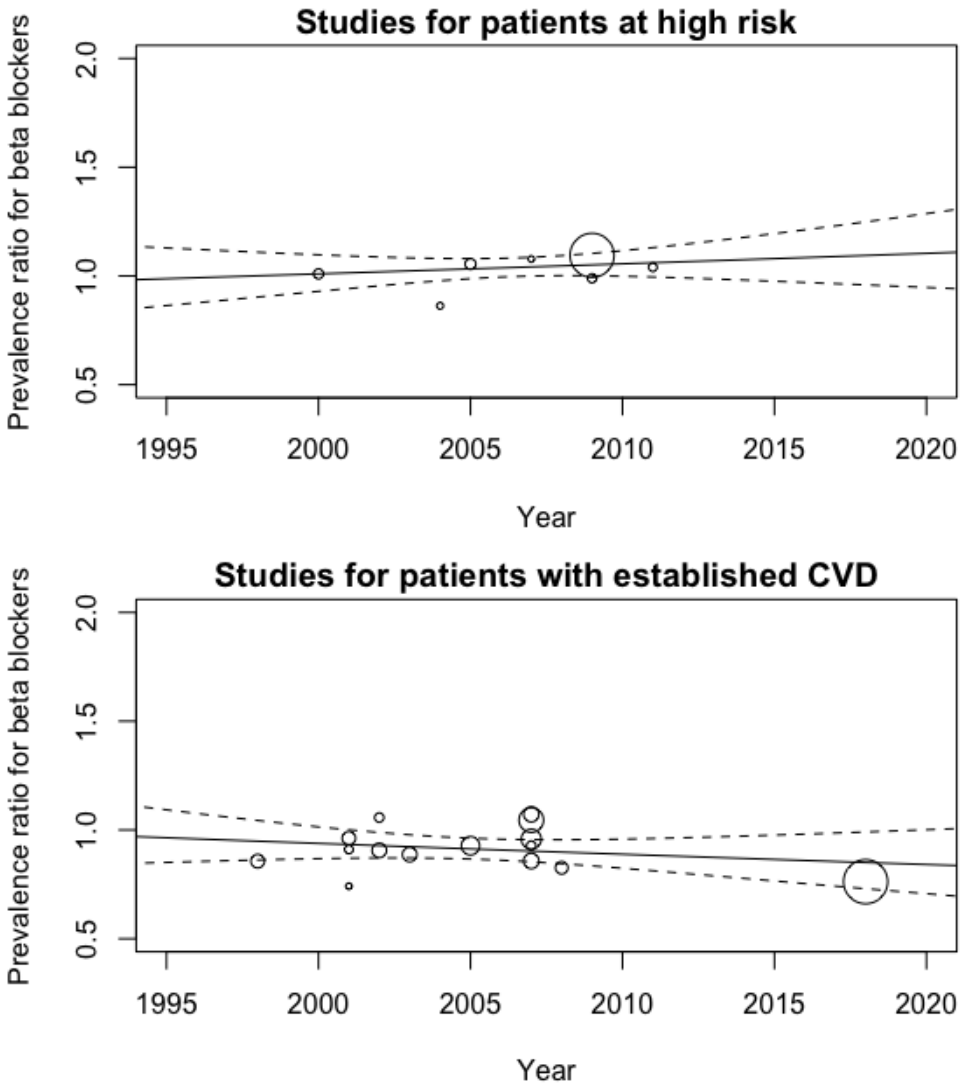
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.

Figure S7. Women-to-men prevalence ratio of statin prescription, stratified by CVD status.



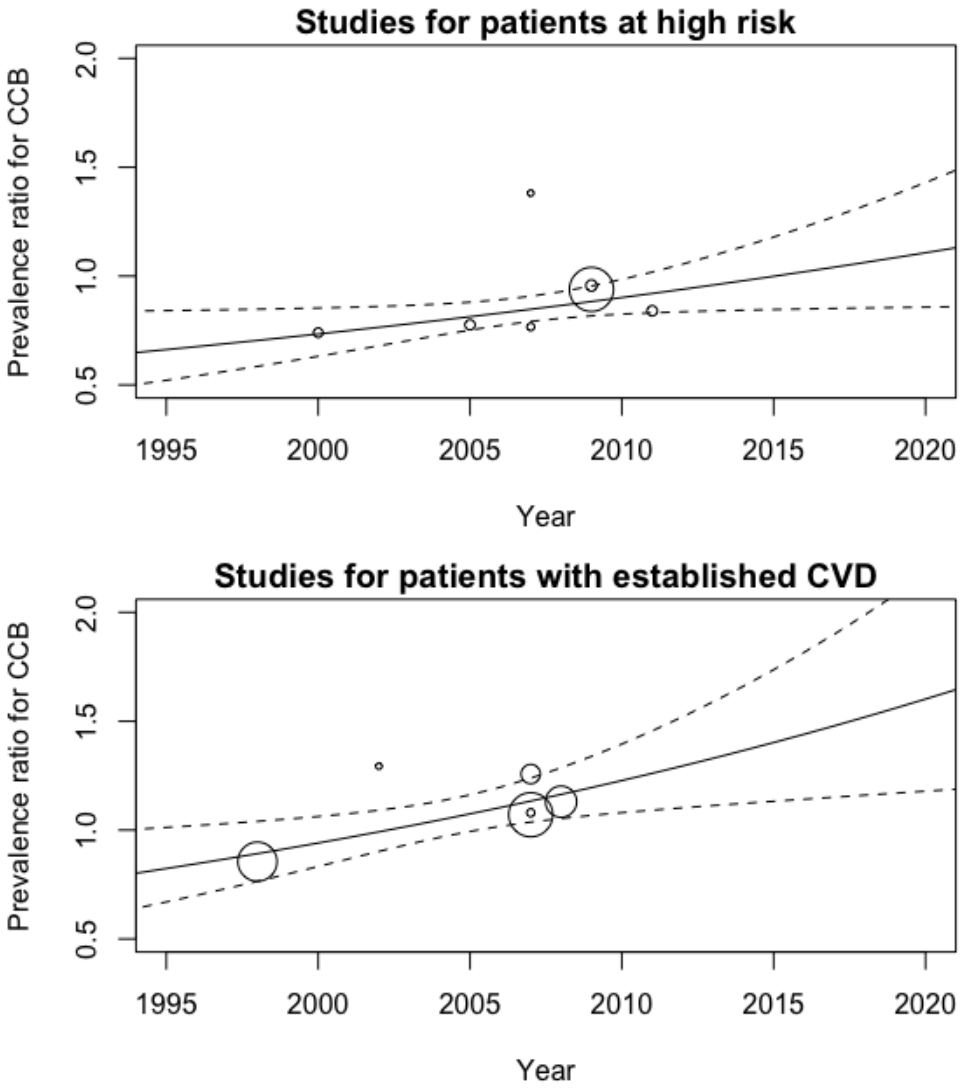
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.

Figure S8. Women-to-men prevalence ratio of beta blocker prescription, stratified by CVD status.



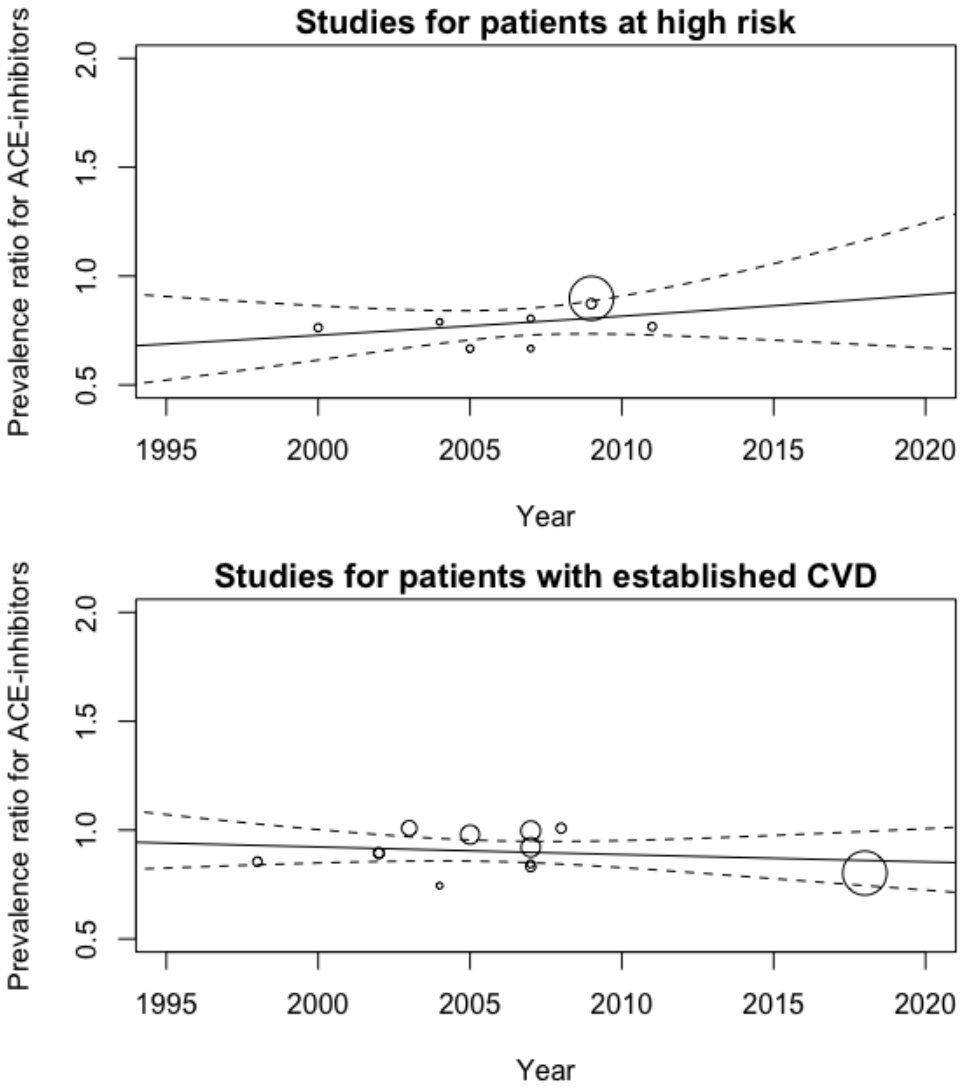
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.

Figure S9. Women-to-men prevalence ratio of calcium channel blocker prescription, stratified by CVD status.



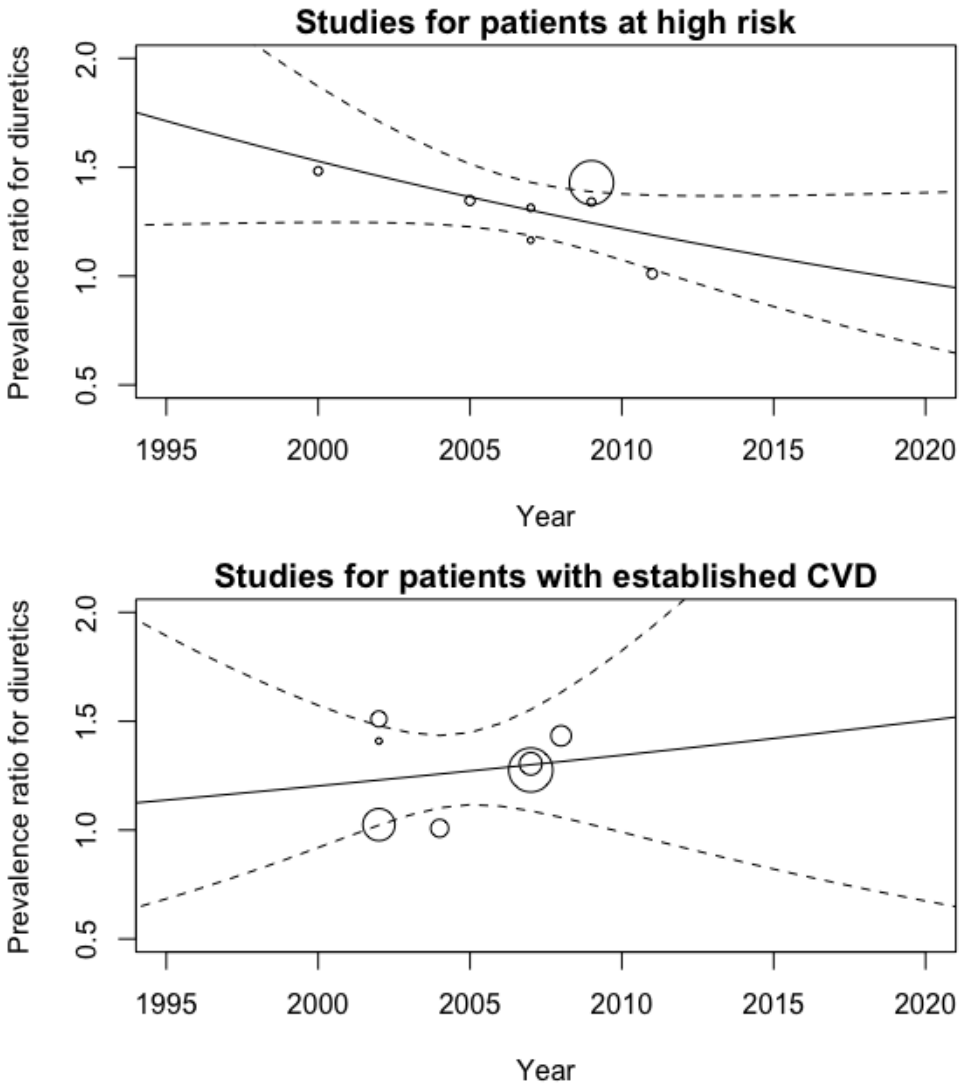
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.

Figure S10. Women-to-men prevalence ratio of ACE-inhibitor prescription, stratified by CVD status.



For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.

Figure S11. Women-to-men prevalence ratio of diuretics prescription, stratified by CVD status.



For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.