

Prognostic Value of Dehydroepiandrosterone Sulfate for Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis

Ting-Ting Wu, MD; Yuan Chen, MD; Yun Zhou, MD; Dilare Adi, PhD; Ying-Ying Zheng, PhD; Fen Liu, MS; Yi-Tong Ma, MD, PhD; Xiang Xie, MD, PhD

Background—The aim of the present study was to estimate the impact of dehydroepiandrosterone sulfate (DHEAS) on the prognosis of patients with cardiovascular disease by performing a systematic review and meta-analysis.

Methods and Results—The Embase, PubMed, Web of Science, CNKI, and WanFang databases were searched up to September 5, 2016, to identify eligible studies. The quality of each study was assessed using the Newcastle-Ottawa Scale. The association between DHEAS, either on admission or at discharge, and cardiovascular disease outcomes were reviewed. The overall risk ratio for the effect of DHEAS on all-cause mortality and fatal and nonfatal cardiovascular events was pooled using a fixed-effects or a random-effects model. The publication bias was evaluated using funnel plots. Twenty-five studies were included for systematic review. The follow-up duration ranged from 1 to 19 years. Eighteen studies were included in the meta-analysis. We found that lower DHEAS levels indicated a significant increased risk for all-cause mortality (risk ratio, 1.47; 95% CI, 1.38-1.56 [P<0.00001]), fatal cardiovascular event (risk ratio, 1.58; 95% CI, 1.30-1.91 [P<0.00001]), and nonfatal cardiovascular event (risk ratio, 1.42; 95% CI, 1.24-1.62 [P<0.0001]) in patients with cardiovascular disease.

Conclusions—Patients with cardiovascular disease who have lower DHEAS levels may have poorer prognosis than those with higher DHEAS levels. (*J Am Heart Assoc.* 2017;6:e004896. DOI: 10.1161/JAHA.116.004896.)

Key Words: cardiovascular disease • dehydroepiandrosterone sulfate • meta-analysis • prognosis • sex hormones • systematic review

D ehydroepiandrosterone (DHEA) and its sulphated ester (DHEAS), working as multifunctional steroids,¹ are mainly produced in the adrenal cortex and converted to testosterone and estradiol in target tissues via androgenconverting enzymes.² DHEA is also synthesized in brain from 17OH pregnenolone and skin.³ It is suggested that DHEAS is a neuroactive steroid that would have a decisive role in the central nervous system, and some studies have established an association between DHEAS levels and degenerative disorders of the nervous system, including Addison's disease, Alzheimer's disease, depression, memory loss, and schizophrenia.⁴ The concentrations of DHEAS are sex related and vary during life.⁵ As both cortisol and DHEAS are synthesized within the adrenal cortex, and it is conceivable that their respective relative contributions to adrenal steroid output might define observed biological action. Furthermore, the cortisol to DHEAS ratio has been found to predict health outcomes better than the level of either hormone alone and in aging,⁶ Alzheimer's disease,⁷ metabolic syndrome,^{8–10} and all-cause mortality (ACM).^{10–13} By far, the strongest associations with the metabolic syndrome were observed in the cortisol / DHEAS ratio by Phillips et al.⁸ As DHEAS and cortisol have opposing effects on the innate immune system, while DHEAS enhances, cortisol suppresses, and the molar ratio of cortisol to DHEAS also increases with age, so it may be an important marker of glucocorticoid function.¹⁴

It is not yet clear whether the physiological decline in DHEA represents a harmful deficiency resulting from aging and the occurrence of degenerative processes or an agerelated adaptation. Several studies have documented that DHEA and DHEAS might be implicated in a broad range of biological abnormalities including obesity, diabetes mellitus, osteoporosis, sexual dysfunction, cancer, and mental disorders, leading to speculation that a relative DHEAS deficiency may contribute to the development of common age-related diseases or diminished longevity.^{15–19} Special interest in the

From the Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China (T.-T.W., Y.C., Y.Z., D.A., Y.-Y.Z., Y.-T.M., X.X.); Xinjiang Key Laboratory of Cardiovascular Disease Research, Urumqi, China (F.L.).

Correspondence to: Xiang Xie, MD, PhD, Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, China. E-mail: xiangxie999@sina.com

Received October 19, 2016; accepted February 24, 2017.

^{© 2017} The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

role of DHEA dates back to the discovery of a relationship between a low serum concentration of DHEA and higher morbidity and mortality due to cardiovascular disease (CVD).^{20–23} These findings were not confirmed by a later study²⁴ and the issue remains controversial. Therefore, we performed a systematic review and meta-analysis to clarify the impact of DHEAS on the prognosis of patients with CVD.

Methods

Search Strategy

Literature searches were performed to identify all relevant and published studies focused on the prognostic value of DHEAS for patients with CVD. Two authors (T.-T.W. and Y.C.) independently searched electronic databases (PubMed, Embase, Web of Science, CNKI, and WanFang) updated on September 5, 2016, using "DHEAS," "mortality," "CV event," and their corresponding index words as keywords.

Inclusion and Exclusion Criteria

Inclusion criteria were the following: (1) cohort studies that evaluated the prognostic value of DHEAS for patients with CVD; (2) studies with a follow-up duration of more than 1 year; (3) studies that reported at least 1 of the following outcomes: ACM, cardiovascular events such as cardiovascular death, myocardial infarction, stroke, heart failure, and readmission; and (4) paper type: original prospective quantitative cohort study (ie, no review, commentary, case reports, editorial). Studies that met any of the following exclusion criteria were excluded: (1) animal or cell line studies; (2) duplicated publications; and (3) manuscripts published in languages other than English or Chinese. Disagreements were resolved by discussion and consensus.

Data Extraction

Data extraction and quality assessment were performed independently by 2 authors (T.-T.W. and Y.C.). The following data were extracted from eligible studies: names of the first authors, publication year, sources of participants, sample sizes, participants' characteristics, follow-up durations, end points with their corresponding hazard ratios (HRs), risk ratios, odds ratios, and 95% CIs, and the confounding factors adjusted for. The corresponding authors of the eligible studies were contacted for detailed information if the necessary data were not reported in the full text of the papers. If no valid data were achieved, then we will exclude this study. The Newcastle-Ottawa Scale, with minor modifications, was used to assess the quality of the included studies. Any

disagreements were resolved by discussion with a third author (Y.Z.) who was blinded to the previous results.

Statistical Analysis

Results reported as count data were presented for ACM, fatal cardiovascular events, and nonfatal cardiovascular events. We extracted the results of the lowest versus highest DHEAS concentrations and used the highest DHEAS category as the reference. If the study reported more than one estimate, only the result of the largest DHEAS difference was included. We transformed risk estimates by taking their natural logarithms and calculated the standard errors as follows: (Ln upper limit–Ln HR)/1.96. We weighted the natural logarithm of the risk estimates by generic inverse variance to account for the sample size and distribution of the included studies. We used Review Manager 5.1 (The Cochrane Collaboration, Oxford, United Kingdom) to analyze the collected data. The results of the included studies were pooled and meta-analyses were carried out using fixed- or random-effects models. Statistical heterogeneity between studies was assessed using the chisquare test with significance set at P<0.10, and heterogeneity was quantified using the l^2 statistic. l^2 values represent the proportion of total variation attributable to heterogeneity rather than chance whereby 0% is no observed heterogeneity and 100% is maximal heterogeneity.

Potential publication bias was evaluated by visual inspection of a funnel plot. A priori sensitivity analyses were defined to evaluate the stability of the pooled estimates and to examine changes in results after excluding specific studies.



Figure 1. The flowchart of article inclusion. CVD indicates cardiovascular disease.

Table 1. Summary of Eligible Studies

Author	Year	Country	Ethnicity	Design	No. of Patients	Age, y	Men, %	Follow-Up	Quality Evaluation
Blum et al ¹²	2013	United States	White	Prospective	231	71±14	59	1 y	6
Phillips et al ¹³	2010	Vietnam	Asian	Retrospective	4255	38.3	100	15 y	8
Maggio et al ²⁵	2007	Italy	White	Retrospective	410	65–92	100	6 у	8
Cappola et al ²⁶	2006	United States	White	Prospective	539	77.6 (66–100)	0	5 y	7
Page et al ²⁷	2008	United States	White	Prospective	32 826	43–69	0	8—9 y	7
Ohlsson et al ²⁸	2010	Sweden	White	Prospective	2644	75.5±3.2	100	4.5 y	7
Shufelt et al ²⁹	2010	United States	White	Prospective	270	64±10	0	9 у	7
Hsu et al ³⁰	2012	Taiwan	Asian	Prospective	200	58.5±13.9	47	38.2 mo	7
Trivedi et al ³¹	2001	United Kingdom	White	Prospective	963	65–76	100	6—10 y	7
Trivedi et al ³¹	2001	United Kingdom	White	Prospective	1171	65–76	0	6—10 y	7
Jansson et al ³²	1998	Sweden	White	Prospective	123	≤70	77	10.5 y	7
Forti et al ³³	2012	Italy	White	Prospective	920	73.7±6.6	45	8 y	8
Jankowska et al ³⁴	2010	Poland	White	Prospective	163	60±10	100	28 mo	8
Jiménez et al ³⁵	2013	United States	White	Prospective	32 826	43–69	0	10 y	6
Sanders et al ³⁶	2010	United States	White	Retrospective	989	85.2	36.5	9 у	7
Feldman et al ³⁷	2001	United States	White	Prospective	1167	40–70	100	8.9 y	7
Ponholzer et al ³⁸	2009	Vienna	White	Prospective	247	75.8	100	5 y	7
Glei et al ³⁹	2006	Taiwan	Asian	Prospective	963	54–91	57.9	3 у	8
Fukai et al ⁴⁰	2011	Japan	Asian	Prospective	97	83±7	0	45 mo	8
Arnlöv et al ⁴¹	2006	United States	White	Prospective	1928	55±12	100	10 y	7
Tivesten et al42	2014	Sweden	White	Prospective	2416	75.4±3.2	100	5 y	8
Güder et al ⁴³	2009	German	White	Prospective	191	64.4	100	859 d	7
Barrett-Connor et al44	1995	United States	White	Prospective	1971	60.4±12.8	52.2	19 y	6
LaCroix et al ⁴⁵	1992	Japan	Asian	Prospective	3775	45–68	100	18 y	6
Haring et al ⁴⁶	2013	German	White	Prospective	254	75.5	100	10 y	7
Cappola et al ⁴⁷	2009	United States	White	Retrospective	950	72.9	49	8 y	7

The subgroup analyses were preplanned for: length of followup, study design, sample size, ethnicity, sex, and DHEAS categories as quartiles. The authors had full access to the data and take responsibility for its integrity. All authors read and agreed to the manuscript as written.

End Point Definition

The explored end points in this meta-analysis are as follows: ACM; fatal cardiovascular events; nonfatal cardiovascular events; and fatal/nonfatal cardiovascular events.

Results

Summary of Eligible Studies

Based on our search criteria, we identified 637 potentially relevant articles. By scanning the titles and abstracts we

excluded 541 articles. A total of 71 studies were excluded for the following reasons: 33 lacked any of our requisite data and 27 were not related to CVD or CVD outcomes. Eleven were excluded based on study design. Overall, 25 cohort studies, with a total of 92 489 CVD patients, were included in our systematic review.^{12,13,25–47} For each of these studies, we extracted items including year of publication, name of the first author, country of origin of the research group, sample number of studies included, design used in the studies, quality evaluation of the studies, follow-up time, confounder for adjustments, DHEAS concentration gradient, and end point. Results of the meta-analysis on the main end point are expressed as HRs and 95% CIs.

A flowchart outlining our literature search is shown in Figure 1. A summary of the characteristics of the eligible studies is given in Table 1. Twenty-one of the included studies were prospective cohort studies, whereas 4 were retrospective studies. For quality assessment, 25 studies were eligible

ories	tomous cutoff values vs high	S logged	tomous cutoff values vs high	63	s Q4	tomous cutoff values /s high	tomous cutoff values vs high	tomous cutoff values /s high	\$ 04
Categ	Dicho	DHE	Dich	01 v	01 v	Dicho	Diche	Dicho	Q1 V
Normalized DHEAS	91.86 µg/dL (49.76– 141.62)	239.8±99.86 μg/dL	50 µg/dL	≤21.6 μg/dL >21.6, ≤39.7 >39.7, ≤67.9 >67.9	27.14 μg/dL 27.14–42.49 42.50–64.08 ≥64.09	3.7 µg/dL	24.7 μg/dL	7.9 μg/dL	61.24 µg/dL 61.24–95.69 95.70–145.45 >145.45
HR	1.6 (0.85–3.8) 1.23 (1.01–1.49)	0.55 (0.43–0.71) 0.4 (0.23–0.7) 0.45 (0.3–0.67)	1.38 (0.84–2.26)	2.05 (1.27–3.32)	1.58 (1.09–2.3)	1.49 (1.17–1.89) 1.61 (1.10–2.38) 1.66 (1.01–2.72)	2.26 (1.08–4.75) 2.43 (1.06–5.56)	2.93 (1.09–7.89) 3.81 (0.91–15.9) 2.18 (0.52–9.05)	Men 1.37 (0.91–2.08) 1.79 (1.03–3.13)
Adjustments	Age, sex, Charlson index	Age and other covariates/fully adjusted/age and fully adjusted	Age, BMI, cancer, log (interleukin 6), education, cognitive function, depression, physical activity, caloric and alcohol intake, smoking, CHD (including angina and MI), CHF, stroke, diabetes mellitus, hypertension, Parkinson disease, peripheral artery disease, asthma, cancer, and COPD	Age, education, race, smoking status, BMI, estrogen use, corticosteroid use, chronic conditions including CHD, CHF, peripheral artery disease, hip fracture, osteoarthritis, theumatoid arthritis, DM, cancer, stroke, and COPD	Age at blood draw, time of blood collection, fasting status at blood collection, menopausal status, parents' history of MI, current postmenopausal hormone use, history of DM, history of hypertension, history of hypercholesterolemia, aspirin use, mean alcohol intake, BMI, physical activity in metabolic equivalent hours	Age, current smoking, BMI, DM, hypertension, Apolipoprotein B to Apolipoprotein A1 ratio, low testosterone, low estradiol	Age, ethnicity, established CVD risk factors	Age, DM, COPD, cardiothoracic ratio, hs-CRP, dialysis duration, albumin creatinine	Age, BP, BMI, cholesterol, current smokers, steroid use, hormone replacement therapy use, history of CVD or cancer
Outcome	Mortality Poor functional outcome	ACM CM OM	ACM	Mortality	W	ACM CM IHD mortality	ACM CM	ACM CM OM	ACM CM
Baseline Diseases	Acute ischemic stroke	÷	:	Disabled women	Postmenopausal women	:	Postmenopausal women with MI	CKD hemodialysis men	:
Year	2013	2010	2007	2006	2008	2010	2010	2012	2001
Author	Blum et al ¹²	Phillips et al ¹³	Maggio et al ²⁵	Cappola et al ²⁶	Page et al ²⁷	Ohlsson et al ²⁸	Shufelt et al ²⁹	Hsu et al ³⁰	Trivedi et al ³¹

Continued

Downloaded from http://ahajournals.org by on October 30, 2024

Table 2. Main Findings of the Eligible Studies

DOI: 10.1161/JAHA.116.004896

Categories	Q1 vs Q4	Q1 vs Q4	Q1 vs Q4	Dichotomous cutoff values Low vs high	Q1 vs Q4	Dichotomous cutoff values	Q1 vs Q4	Dichotomous cutoff values	Dichotomous cutoff values	Dichotomous cutoff values
Normalized DHEAS	38.28 µg/dL 38.28-57.41 57.42-80.03 >80.04	176.07 µg/dL (145.45– 202.87)	≤57.42 μg/dL 57.43–86.51 86.52–135.88 ≥135.89	6.48 µg/dL (3.60–13.15)	<42 µg/dL 42–65.2 65.6–101 >101.5	55.5 μg/dL ±41.4	2.7–15.9 μg/dL 16.0–23.4 23.5–33.0 33.1–123	50 µg/dL	54.5 µg/dL	43 µg/dL
HR	Women 0.87 (0.53–1.45) 0.84 (0.41–1.72)	1.79 (0.84–3.70)	1.45 (0.98–2.17)	1.95 (1.23–3.10)	1.44 (0.93–2.23)	1.46 (1.03–2.05)	1.97 (1.12–3.48)	1.85 (1.05–3.23)	1.41 (1.31–1.52)	4.42 (1.51–12.9)
Adjustments	Age, BP, BMI, cholesterol, current smokers, steroid use, hormone replacement therapy use, history of CVD or cancer	Univariate	Age and baseline presence of smoking, BMI, IHD, disability, frailty (not included in the model for women stratified by frailty status), preexisting major diseases (not included in the model for women stratified by preexisting major diseases), Geriatric Depression Scale, Mini-Mental State Examination, and hs-CRP	Beck Depression Inventory, serum total testosterone, LVEF, BMI, CHF etiology, CAD vs non-CAD, plasma NT-proBNP, eGFR, NYHA class, hemoglobin, age, DM Variables selected based on stepwise approach	Age, ancestry, menopausal status, hormone use, smoking, date of blood collection, BMI, aspirin use, alcohol intake, physical activity, Atternative Healthy Eating Index, history of DM, hypertension, and CHD, or revascularization, glycated hemoglobin, and total/HDL-C	All factors in the full model plus mean age, BMI, and cholesterol. CVD or CHD and CBD were added separately	Age, race, married, education, employed, serum cholesterol, low HDL-C, obesity, DM, hypertension, cigarette smoking, passive smoking, home and work moderate to vigorous physical activity, and alcohol consumption	No mention	Various indicators of health status in 2000	Age, nutritional parameters, functional parameters, and prevalent disease
Outcome	ACM CM	CM	ACM	CM and unplanned hospitalization	Ischemic stroke	CVD	Я	CVD	Mortality	ACM
Baseline Diseases	:	Acute MI	:	CHF	÷	÷	÷	:	:	:
Year	2001	1998	2012	2010	2013	2010	2001	2009	2006	2011
Author		Jansson et al ³²	Forti et al ³³	Jankowska et al ³⁴	Jiménez et al ³⁵	Sanders et al ³⁶	Feldman et al ³⁷	Ponholzer et al ³⁸	Glei et al ³⁹	Fukai et al ⁴⁰

Continued

Table 2. Continued

Downloaded from http://ahajournals.org by on October 30, 2024

DOI: 10.1161/JAHA.116.004896

Categories	Per 1 SD increase in log DHEAS	Per SD increase	DHEAS per 10 µg/dL	A 50-µg/dL decrease in risk ratio	100-µg/dL difference	Variability (per Q increment)	Variability (per SD)
Normalized DHEAS	24.50±19.14 μg/dL	7.1±4.6 μg/dL	73 (36–131) µg/dL	154 µg/dL	5-65 μg/dL 66-92 93-114 115-140 141-277	99.52 (70.81–46.22) μg/dL	0.82 (0.51–1.2) µg/dL
HR	1.02 (0.90–1.15)	0.87 (0.78–0.98) 0.9 (0.79–1.02)	0.97 (0.91–1.03)	0.93 (0.9–0.95) 0.94 (0.84–1.03) 0.96 (0.85–1.05)	0.72 (0.45–1.14)	1.18 (0.96–145) 1.00 (0.82–1.22)	1.89 (1.47–2.43)
Adjustments	Age, smoking, systolic and diastolic BP, hypertension treatment, total cholesterol– HDL-C ratio, DM, and BMI	Age, Osteoporotic Fractures in Men study site, morning sample, current smoking, BMI, DM, hypertension, Apolipoprotein B and Apolipoprotein A1. Log10-transformed values of DHEA, DHEAS, BMI, and hs-CRP	Age, NYHA class, free testosterone: renal function, atrial fibrillation, systolic BP, C- reactive protein, NT-proBNP, intake of diuretics, cortisol; for DHEAS: renal function, atrial fibrillation, total cholesterol, NT-proBNP, intake of diuretics, intake of β-blockers; for sex hormone–binding globulin: renal function, atrial fibrillation, NT-proBNP, intake of angiotensin- converting enzyme inhibitor, intake of statin, cortisol	Age, BP, smoking, total cholesterol, BMI, fasting plasma glucose, and replacement estrogen	Systolic BP, serum cholesterol, subscapular skinfold, serum glucose, diabetes mellitus medication, alcohol, physical activity index	Age, BMI, smoking, total cholesterol, HDL- C, type 2 DM, systolic BP, and antihypertensive medication	Age, sex, race, CVD, pulmonary disease, DM, cancer, depression
Outcome	CVD	CBD	ACM	ACM CM IHD mortality	IW	ACM CVD	Mortality
Baseline Diseases	:	:	Heart failure	÷	:	:	:
Year	2006	2014	2009	1995	1992	2013	2009
Author	Arnlöv et al ⁴¹	Tivesten et al ⁴²	Güder et al ⁴³	Barrett-Connor et al ⁴⁴	LaCroix et al ⁴⁵	Haring et al ⁴⁶	Cappola et al ⁴⁷

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone; DHS, nacedial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OM, other mortality; Q, quartile.

Downloaded from http://ahajournals.org by on October 30, 2024

Table 2. Continued

			Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio] SI	<u>Weight</u>	IV, Fixed, 95% C	I IV. Fixed, 95% CI
Anna C Phillips [13]	0.55 0.0816	5 14.4%	1.73 [1.48, 2.03]	•
Anne R. Cappola [26]	0.7178 0.2443	3 1.6%	2.05 [1.27, 3.31]	
ChrisandraShufelt [29]	0.8154 0.3767	0.7%	2.26 [1.08, 4.73]	
Claes Ohlsson [28]	0.3988 0.1234	6.3%	1.49 [1.17, 1.90]	-
Claudine A.Blum [12]	0.47 0.4413	0.5%	1.60 [0.67, 3.80]	
D.P.Trivedi [31]	0.3148 0.2087	2.2%	1.37 [0.91, 2.06]	
D.P.Trivedi [31]	-0.1393 0.2529	1.5%	0.87 [0.53, 1.43]	-+_
Dana A.Glei [39]	0.3436 0.0375	68.2%	1.41 [1.31, 1.52]	
Heng-Jung Hsu [30]	1.076 0.505	5 0.4%	2.93 [1.09, 7.89]	
Marcello Maggio [25]	0.3221 0.2533	1.5%	1.38 [0.84, 2.27]	
Paola Forti [33]	0.3716 0.1999	2.4%	1.45 [0.98, 2.15]	
Shiho Fukai [40]	1.486 0.548	0.3%	4.42 [1.51, 12.94]	
Total (95% CI)		100.0%	1.47 [1.38, 1.56]	
Heterogeneity: Chi ² = 18	.90, df = 11 (P = 0.06); l ²	= 42%		
Test for overall effect: Z	= 12.45 (P < 0.00001)		F	Favours [experimental] Favours [control]

Figure 2. The relationship between dehydroepiandrosterone sulfate and all-cause mortality.

and ranked according to their sum scores (Table 1), of which 21 studies were graded as "good" (scores >6) and 4 as "moderate" (scores \leq 6) quality.

Main Findings of Eligible Studies

Table 2 shows the main findings of all eligible studies. Seven studies used DHEAS concentrations as a continuous variable with different variability (per SD in DHEAS, per quartile increment in DHEAS, per 10-, 50-, and 100-µg/dL difference in DHEAS), investigating the relationship between DHEAS and ACM and fatal and nonfatal cardiovascular events, respectively.^{41–47} Finally, in 18 studies, the authors used the lowest versus highest or dichotomous cutoff values of DHEAS concentrations as categories and used the highest DHEAS category as the reference, and calculated the data risk



Figure 3. The relationship between dehydroepiandrosterone sulfate and fatal cardiovascular events.

				Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Fixed, 95% C	I IV, Fixed, 95% Cl
Anton Ponholzer [38]	0.6152	0.289	5.5%	1.85 [1.05, 3.26]	
Claes Ohlsson [28]	0.5068	0.2535	7.1%	1.66 [1.01, 2.73]	
Claudine A.Blum [12]	0.207	0.1005	45.4%	1.23 [1.01, 1.50]	•
Henry A. F [37]	0.678	0.2881	5.5%	1.97 [1.12, 3.46]	
Jason L.Sanders [36]	0.3784	0.178	14.5%	1.46 [1.03, 2.07]	-
Jimenez MC [35]	0.3646	0.2231	9.2%	1.44 [0.93, 2.23]	
John H.Page [27]	0.4574	0.1894	12.8%	1.58 [1.09, 2.29]	-
Total (95% CI)			100.0%	1.42 [1.24, 1.62]	•
Heterogeneity: Chi ² = 4.	90, df = 6 (P = 0.56	6); l ² = 0	%		
Test for overall effect: Z	= 5.14 (P < 0.000	01)		F	avours [experimental] Favours [control]



Table 3. Subgroup Analysis (ACM)

				Heterogen	eity	Meta-Analysi	S
Subgroup	Design	No. of Studies	Sample Sizes	l ²	P Value	HR	95% CI
Study design	Prospective	9	7998	36	<0.0001	1.43	1.34–1.53
	Retrospective	2	4665	0	<0.0001	1.70	1.46–1.98
Sample size	<1000	8	3630	21	<0.0001	1.44	1.34–1.54
	≥1000	3	9033	72	0.02	1.43	1.07–1.91
Follow-up	<4 y	4	1491	54	0.01	1.95	1.17–3.25
	≥4 y	7	11 172	0	<0.0001	1.58	1.42–1.76
Ethnicity	Asian	4	5515	73	<0.0001	1.69	1.32–2.16
	Non-Asian	7	7148	9	<0.0001	1.46	1.26–1.69
Studies with DHEAS	Yes	4	7848	0	0.03	1.39	1.12–1.73
categories as quartiles	No	7	4815	0	<0.0001	1.43	1.34–1.54

ACM indicates all-cause mortality; DHEAS: dehydroepiandrosterone sulfate; HR, hazard ratio.

estimates (HRs/odds ratios), regression coefficients, and 95% CIs. Eleven studies investigated the relationship between DHEAS and ACM, 6 investigated fatal cardiovascular events, and 7 investigated nonfatal cardiovascular events. The confounding factors adjusted for among the eligible studies varied, including age, smoking, systolic and diastolic blood pressure, hypertension, high-density lipoprotein cholesterol, total cholesterol, diabetes mellitus, BMI, high serum C-reactive

protein, Apolipoprotein B to Apolipoprotein A1 ratio, and low testosterone.

DHEAS and Outcomes

DHEAS and ACM

There were 11 studies that reported positive associations between low DHEAS concentrations and ACM. Meta-analysis

Table 4. Subgroup Analysis (Fatal Cardiovascular Event)

				Heterogeneity		Meta-Analysis	
Subgroup	Design	No. of Studies	Sample Sizes	l ²	P Value	HR	95% CI
Sample size	<1000	4	1556	0	0.0003	2.01	1.38–2.94
	≥1000	3	8070	22	0.001	1.45	1.16–1.81
Ethnicity	Asian	2	4455	36	0.003	1.55	1.16–2.08
	Non-Asian	4	5171	7	< 0.0003	1.60	1.24–2.06
Studies with DHEAS	Yes	3	2257	0	0.05	1.45	0.99–2.12
categories as quartiles	No	4	7369	0	<0.0001	1.62	1.30–2.03

DHEAS indicates dehydroepiandrosterone sulfate; HR, hazard ratio.

Table 5. Subgroup Analysis (Nonfatal Cardiovascular Event)

				Heterogenei	ty	Meta-Analysis	
Subgroup	Design	No. of Studies	Sample Sizes	l ²	P Value	HR	95% CI
Sample size	<1000	3	1467	8	0.0009	1.32	1.12–1.56
	≥1000	4	69 463	10	< 0.0001	1.61	1.29–2.02
Studies with DHEAS	Yes	3	66 819	0	0.0003	1.60	1.24–2.06
categories as quartiles	No	4	4111	0	0.0001	1.35	1.16–1.58

DHEAS indicates dehydroepiandrosterone sulfate; HR, hazard ratio.

Downloaded from http://ahajournals.org by on October 30, 2024

results showed that CVD with low DHEAS was associated with a 47% higher risk of future mortality events (HR, 1.47; 95% Cl, 1.38-1.56 [P<0.00001] (Figure 2).

DHEAS and fatal/nonfatal cardiovascular events

Six studies investigated deficient DHEAS level and fatal cardiovascular events, 13,28-32 7 studies 12,27,28,35-38 investigated low DHEAS and nonfatal cardiovascular events, and 1 study³⁴ reported DHEAS with fatal/nonfatal cardiovascular events separately. In the meta-analysis, the pooled estimates

for the lowest compared with the highest category of baseline DHEAS indicated a significant increased risk for fatal cardiovascular events without heterogeneity ($l^2=0\%$): pooled risk ratio, 1.58 (95% Cl, 1.30–1.91; P<0.00001 [Figure 3]).

The pooled estimate for nonfatal cardiovascular events resulted in a slightly higher association: risk ratio, 1.42 (95% Cl, 1.24–1.62; *P*<0.00001 [Figure 4]), with no heterogeneity $(l^2=0\%)$. The HR for the fatal/nonfatal cardiovascular events resulted in a higher association: risk ratio 1.95 (95% Cl, 1.23-3.10; *P*=0.005).

Odds Ratio Odds Ratio Odds Ratio Odds Ratio Odds Ratio Study or Subgroup log[Odds Ratio] SE Weight N. Random. 95% CI N. Random. 95% CI OrtsrandrsShufel (29) 0.7178 0.2443 18.2% 2.05 [1.27, 3.31] Image: Composition of the compositi						
Study or Subgroup leg(3dds Ratio) SE Weight //. Random, 35% CL //. N. Random, 35% CL //. Random, 35% C					Odds Ratio	Odds Ratio
1.1.1 female ACM Anne R. Capoble (26) 0.7178 0.2443 16.2% 2.05 [1.27, 3.31] ChrisandraShufet [29] 0.8154 0.3767 13.3% 2.26 [1.08, 4.73] D.P.Triveti [31] 0.101 0.1393 0.2527 17.8% 0.879 0.243 16.2% 1.79 [1.12, 2.45] Heterogeneity: Tat ² = 0.17, Ch ² = 1.13, df = 4 (P = 0.03); P = 64% Test for overall effect Z = 2.44 (P = 0.01) 1.1.2 female fatal CV event ChrisandraShufet [29] 0.8879 0.4233 11.9% 2.42 [1.06, 5.57] D.P.Triveti [31] 0.11 0.11 0.11 0.10 Test for overall effect Z = 2.64 (P = 0.02); P = 64% Test for overall effect Z = 0.63 (P = 0.06); P = 72% Test for overall effect Z = 0.63 (P = 0.06); P = 72% Test for overall effect Z = 0.63 (P = 0.02); P = 61% 0.01 0.1 1 0.1 Test for overall effect Z = 0.01 Test for overall effect Z = 2.50 (P = 0.01) Test for overall effect Z = 2.50 (P = 0.02); P = 61% 0.01 0.1 0.1 Test for overall effect Z = 2.50 (P = 0.01) Test for overall effect Z = 2.50 (P = 0.02); P = 0% Test for overall effect Z = 2.50 (P = 0.02); P = 0% 1.2.3 female non-fatal CV event Jimenez MC [35] 0.3646 0.2231 4.6% 1.44 [0.43, 2.23] John H Pag (27) 0.4574 0.184 6.4% 1.58 [1.09, 2.29] Vertex for overall effect Z = 2.50 (P = 0.004) 1.2.4 male ACM Anna C Philips [13] 0.550 0.816 34.4% 1.73 [1.48, 2.03] Chiese Ohisson [28] 0.4762 0.104 6.1% 1.49 [1.17, 1.90] 1.2.5 male fatal CV event Jimenez MC [36] 0.1 0.1 0.1 0.1 1.2 finale and MACM Anna C Philips [13] 0.4762 0.194 6.1% 1.49 [1.17, 2.06] 4.149 [1.11, 2.01] 1.2.5 male fatal CV event Anna C Philips [13] 0.4762 0.194 6.1% 1.58 [1.40, 2.79] Heterogeneity: Ch ² = 0.3, df = 2 (P = 0.75); P = 0% Test for overall effect Z = -3.72 (P = 0.0001) 1.2.5 male fatal CV event Anna C Philips [13] 0.4762 0.194 6.1% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 0.34, df = 2 (P = 0.39); P = 0% Test for overall effect Z = -3.72 (P = 0.0002) 1.2.6 male non-fatal CV event Anton Ponhizer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Chiese Ohisson [28] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Chiese Ohisson [28] 0.6152 0.289 2	Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% C	I IV. Random, 95% Cl
Anne R. Cappola [26] 0.7178 0.2443 18.2% 2.05 [1.27, 3.31] O.P. Tived [31] 0.1390 0.252 17.8% 0.87 [0.53, 1.43] D.P. Tived [31] 0.527 0.2943 16.2% 1.70 [0.95, 3.02] Shibo Fuka [40] 1.488 0.548 8.8% 4.42 [1.51, 1.2.94] Subtotal (5% C) 7.47 ± 1.1.3, df = 4 ($P = 0.03$); $P = 64\%$ Test for overall effect $Z = 2.44$ ($P = 0.01$) 1.1.2 female fatal CV event ChrisandraShufet [29] 0.8879 0.4233 11.9% 2.43 [1.06, 5.57] D.P. Tived [31] 0.174 = 0.8679 0.4233 11.9% 2.43 [1.06, 5.57] D.P. Tived [17] 0.174 = 0.8679 0.4233 11.9% 2.43 [1.06, 5.57] D.P. Tived [17] 0.174 = 0.360, df = 1 ($P = 0.06$); $P = 72\%$ Test for overall effect: $Z = 2.63$ ($P = 0.53$) Total (95% C) 1.074 = 0.500, df = 6 ($P = 0.02$); $P = 61\%$ Test for overall effect: $Z = 2.53$ ($P = 0.61$) 100.0% 1.67 [1.12, 2.48] Heterogeneity: Tat ² = 0.17; Ch ² = 1.520, df = 6 ($P = 0.02$); $P = 61\%$ Test for overall effect: $Z = 2.53$ ($P = 0.61$) SE Weight IV. Fixed, 95% Cl 1.23 female non-fatal CV event Jimenex MC [35] 0.3646 0.2231 4.6% 1.44 [0.93, 2.23] John H.Page [27] 0.4674 0.1984 6.4% 1.58 [1.09, 2.29] Subtotal (95% Ci) 1.00[Odds Ratio] SE Weight IV. Fixed, 95% Cl 1.2.3 female non-fatal CV event Jimenex MC [35] 0.3646 0.2231 4.6% 1.49 [1.17, 1.00] Test for overall effect: $Z = 2.90$ ($P = 0.024$) 1.10% 1.52 [1.15, 2.02] Heterogeneity: Ch ² = 0.13, df = 1 ($P = 0.75$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.024$) 1.24 male ACM Anna C Philips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Marcelo Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.42, 2.27] Pada Forti [33] 0.542 0.2823 2.2% 1.15 [0.66, 2.00] Marcelo Maggio [26] 0.3224 0.2533 3.6% 1.38 [1.04, 2.77] Pada Forti [31] 0.3148 0.2087 5.3% 1.37 [0.45, 2.06] Marcelo Maggio [25] 0.3224 0.2583 3.6% 1.48 [1.01, 2.36] D.P. Tived [31] 0.542 0.282 2.2% 2.2% 1.75 [1.65, 1.26] Marcelo Maggio [26] 0.3242 0.2582 2.2% 1.55 [1.40, 1.78] Heterogeneity: Ch ² = 0.35, df = 4 ($P = 0.47$); $P = 0\%$ Test for overall effect: $Z = 3.72$ ($P = 0.300$); $P = 0\%$ Test for overall effect:	1.1.1 female ACM					
ChriandraShulet [29] 0.8154 0.3767 13.3% 2.28 [1.08, 4.73] Paola Fort [31] 0.1390 0.2527 17.8% 0.87 [0.53, 1.43] Paola Fort [33] 0.5277 0.2843 16.2% 1.70 [0.55, 3.02] Shiho Fuke [40] 1.486 0.548 6.8% 4.42 [1.51, 1.294] Subtotal (85% CI) 4.486 0.484 8.8% 4.42 [1.51, 1.294] Faterogeneity: Tat ² = 0.17; Cht ² = 1.1, 3, df = 4 (P = 0.03); P = 64% Test for overall effect: Z = 2.44 (P = 0.01) 1.1.2 female fatal CV event ChriandraShulet [29] 0.8879 0.4233 11.9% 2.43 [1.06, 5.57] D.P.Trived [31] 0.17; Cht ² = 1.5.0, df = 1 (P = 0.06); P = 72% Test for overall effect: Z = 0.63 (P = 0.02); P = 61% Lest for overall effect: Z = 0.63 (P = 0.02); P = 61% Lest for overall effect: Z = 0.63 (P = 0.02); P = 61% Lest for overall effect: Z = 0.63 (P = 0.02); P = 61% Lest for overall effect: Z = 0.63 (P = 0.02); P = 0% Test for overall effect: Z = 0.63 (P = 0.02); P = 0% Study or Subgroup Leg(Odds Ratio) SE Weight IV. Fixed, 95% CI 1.2.3 female non-fatal CV event Jimenez MC [35] 0.3646 0.2231 4.6% 1.44 [0.83, 2.23] John H-Page [27] 0.4574 0.1894 6.4% 1.58 [1.09, 2.29] Subtotal (95% CI) 10.04574 0.1894 6.4% 1.58 [1.09, 2.29] Subtotal (95% CI) 1.10 (10 (P = 0.75); P = 0% Test for overall effect: Z = 2.90 (P = 0.004) 1.2.4 male non-fatal CV event Jimenez MC [36] 0.3846 0.2231 4.6% 1.44 [1.17, 1.90] D.P.Trivet [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcelio Meggio [26] 0.3221 0.253 3.6% 1.38 [0.84, 2.27] Paola Fort [33] 0.1398 0.2222 2.29% 1.15 [0.66, 2.00] 1.2.5 male fatal CVevent Anna C Phillips [13] 0.41 (P = 0.47); P = 0% Test for overall effect: Z = 7.52 (P = 0.0001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.41 (P = 0.47); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4762 0.194 4.61% 1.416 [1.10, 2.36] D.P.Trivet [31] 0.582 0.289 2.7% 1.85 [1.05, 3.26] Clase Ohisson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Heterogeneity: Chf ² = 0.34, df = 2 (P = 0.84); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI)	Anne R. Cappola [26]	0.7178	0.2443	18.2%	2.05 [1.27, 3.31]	
D.P. Inved [31] - 0.139 0.2829 17.8% 0.87 (0.28, 1.43) Paola Fort [33] 0.2877 0.284 16.2% 1.70 [0.95, 3.02] Shibo Fuka [40] 1.686 0.548 8.8% 4.42 [1.51, 1.294] Subtoal (8% C) - 74.4% 1.79 [1.12, 2.45] Heterogeneity: Tat" = 0.17; Chi" = 11.13, df = 4 ($P = 0.03$); $P = 64\%$ Test for overall effect: $Z = 2.44 (P = 0.01)$ 1.1.2 female fatal CV event ChrisandraShufet [29] 0.8879 0.4233 11.9% 2.43 [1.06, 5.57] D.P. Trived [31] - 0.1744 0.3867 Heterogeneity: Tat" = 0.17; Chi" = 3.0, df = f ($P = 0.06$); $P = 72\%$ Test for overall effect: $Z = 2.63 (P = 0.53)$ Total (95% C) - 0.144 0.3867 Heterogeneity: Tat" = 0.17; Chi" = 15.20, df = 6 ($P = 0.02$); $P = 61\%$ Test for overall effect: $Z = 2.53 (P = 0.01)$ Test for suborau differences: Chi" = 0.18, df = 1 ($P = 0.67$); $P = 0\%$ Test for overall effect: $Z = 2.53 (P = 0.01)$ Test for suborau differences: Chi" = 0.18, df = 1 ($P = 0.67$); $P = 0\%$ Test for overall effect: $Z = 2.53 (P = 0.01)$ Test for suborau differences: Chi" = 0.18, df = 1 ($P = 0.67$); $P = 0\%$ Test for overall effect: $Z = 2.90 (P = 0.024)$ 1.2.3 female non-fatal CV event Jimenez MC [35] 0.3846 0.2231 4.6% 1.44 [0.93, 2.23] John H-Page [27] 0.4574 0.1946 6.4% 1.58 [1.09, 2.29] Subtotal (95% C) - 1.01 df = 1 ($P = 0.75$); $P = 0\%$ Test for overall effect: $Z = 2.90 (P = 0.004)$ 1.2.4 male ACM Anna C Philips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Test for overall effect: $Z = 2.90 (P = 0.047)$; $P = 0\%$ Test for overall effect: $Z = 2.90 (P = 0.047)$; $P = 0\%$ Test for overall effect: $Z = 2.90 (P = 0.047)$; $P = 0\%$ Test for overall effect: $Z = 2.90 (P = 0.047)$; $P = 0\%$ Test for overall effect: $Z = 3.72 (P = 0.024)$; $P = 0\%$ Test for overall effect: $Z = 3.72 (P = 0.002)$ 1.2.5 male fastal CV event Anton Ponhozer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Class Ohisson [29] 0.5680 0.2381 2.8\% 1.49 [1.17, 2.01] 1.2.5 male fastal CV event Anton Ponhozer [38] 0.6152 0.289 2.7\% 1.85 [1.05, 3.26] Class Ohisson [29] 0.5780 0.2881 2.8\% 1.49 [1.12, 2.47] Heteroge	ChrisandraShufelt [29]	0.8154	0.3767	13.3%	2.26 [1.08, 4.73]	
Patient Patient (a) $0.227 0.243 ext{ b} 0.25 ext{ b} 1.70 ext{ b} 0.302 ext{ b} 3.86 ext{ b} 4.22 ext{ b} 3.82 ext{ b} 4.42 ext{ b} 3.72 ext{ b} 1.72 ext{ b} 1.72 ext{ b} 3.86 ext{ b} 4.42 ext{ b} 3.72 ext{ b} 1.72 ext{ b} 1.72 ext{ b} 3.86 ext{ b} 1.72 ext{ b} $	D.P. Trivedi [31]	-0.1393	0.2529	17.8%	0.87 [0.53, 1.43]	1
Simp Tube (eq.) Simp	Paola Forti [33]	0.5277	0.2943	16.2%	1.70 [0.95, 3.02]	
Subtool (95% C) 1.1.2 female fatal CV event ChrisendraShufett [29] 0.8879 0.4233 11.9% 2.43 [1.06, 5.57] D.P.Trivedi [31] 0.1744 0.3859 13.7% 0.84 [0.41, 1.72] Subtotal (95% C) D.P.Trivedi [31] 0.1744 0.3650 13.7% 0.84 [0.41, 1.72] Subtotal (95% C) 1.2.5 Mathematical CV event 1.2.6 Mathematical CV event 1.2.6 Mathematical CV event 1.2.7 Mathematical CV event 1.2.3 female non-fatal CV event 1.2.4 male ACM Arma C Phillips [13] 0.3946 0.2231 4.6% 1.44 [0.93, 2.23] John H-Page [27] 1.2.4 male ACM Arma C Phillips [13] 0.3946 0.2231 4.6% 1.44 [0.93, 2.23] John H-Page [27] 0.3946 0.2231 4.6% 1.44 [0.93, 2.23] John H-Page [27] 0.4574 0.1894 6.4% 1.58 [1.09, 2.29] Subtotal (95% C) 1.2.4 male ACM Arma C Phillips [13] 0.3946 0.2231 4.6% 1.44 [0.93, 2.23] John H-Page [27] 0.4574 0.1894 6.4% 1.73 [1.48, 2.03] Claes Ohisson [28] 0.3948 0.1234 15.1% 1.49 [1.17, 1.90] P.Trivedi [31] 0.3948 0.2232 2.9% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3240 0.2067 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3240 0.207 5.3% 1.49 [1.40, 1.79] Heterogeneity: Chi ² = 0.33, df = 4 (P = 0.47); P = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CV event Arma C Phillips [13] 0.4 0.1531 9.8% 149 [1.11, 2.01] Claes Ohisson [28] 0.4762 0.1944 6.1% 1.51 [1.10, 2.36] D.P.Trivedi [31] 0.4 0.1531 9.8% 149 [1.11, 2.01] Claes Ohisson [28] 0.4762 0.1944 6.1% 1.51 [1.10, 2.36] D.P.Trivedi [31] 0.4 0.1531 9.8% 149 [1.11, 2.01] Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CV event Arma C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.51, 1.32, 1.41 [1.32, 3.41] 4.57 [1.42, 3.46] D.P.Trivedi [31] 0.566 0.2583 5.6% 1.46 [1.01, 2.73] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.98); I ² = 0% Test for overall effect: Z = 7.372 (P = 0.0002) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 0.4, df = 12 (P = 0.58); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.0000) 100.0% 1.59 [1.45, 1.75] Favours experimental Favours experimental Favours experimental Favo	Shino Fukai (40) Subtotal (95% CI)	1.400	0.546	0.0%	4.42 [1.51, 12.94]	•
The toperate in the transmission of transmissic transmission of transmission of t	Heterogeneity: $Tau^2 = 0.1$	7: Chi2 = 11 13 df	- 4 (P -	0 03). 12 =	64%	•
1.12 female final CV event ChrisandraShufel [29] 0.8879 0.4233 11.9% 2.43 [1.06, 5.57] D.P.Trivedi [31] -0.1744 0.3659 13.7% 0.84 [0.41, 1.72] Subtotal (95% CI)	Test for overall effect: Z =	= 2.44 (P = 0.01)	- 4 (r -	0.03), 1 =	04 78	
ChrisandraShufel [29] 0.847 0.423 11.9% 2.43 [1.06, 5.7] D.P.Trvedi [31] -0.174 0.3659 13.7% 0.84 [0.41, 1.72] Subtotal (95% CI) 25.6% 1.40 [0.48, 3.96] Heterogeneity: Tau ² = 0.17; Ch ² = 3.60, df = 1 ($P = 0.06$); $P = 72\%$ Test for overall effect: $Z = 0.63$ ($P = 0.53$) Total (95% CI) 100.0% 1.67 [1.12, 2.48] Heterogeneity: Tau ² = 0.17; Ch ² = 15.20, df = 6 ($P = 0.02$); $P = 61\%$ Test for overall effect: $Z = 50.63$ ($P = 0.01$) Test for overall effect: $Z = 50.63$ ($P = 0.01$) Test for overall effect: $Z = 50.63$ ($P = 0.01$) Test for overall effect: $Z = 50.63$ ($P = 0.01$) Test for overall effect: $Z = 2.90$ ($P = 0.02$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.75$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.075$); $P = 0\%$ Test for overall effect: $Z = 7.52$ ($P = 0.0021$) 1.25 male fatal CVevent Anna C Phillips [13] 0.3148 0.2823 2.9\% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2.7% 1.58 [1.40, 1.79] Heterogeneity: Ch ² = 3.53, df = 4 ($P = 0.47$); $P = 0\%$ Test for overall effect: $Z = 7.52$ ($P = 0.0021$) 1.25 male fatal CVevent Anna C Phillips [13] 0.6152 0.289 2.7\% 1.55 [1.40, 1.79] Heterogeneity: Ch ² = 0.21, df = 2 ($P = 0.96$); $P = 0\%$ Test for overall effect: $Z = 4.09$ ($P < 0.0001$) 1.26 moveral effect: $Z = 3.72$ ($P = 0.0002$) Total (95% CI) 9.1% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 0.21, df = 2 ($P = 0.96$); $P = 0\%$ Test for overa	1.1.2 female fatal CV ev	ent				
D.P.Trivedi [31] -0.1744 0.3659 13.7% 0.84 [0.41, 1.72] Subtotal (89% CI) -1.744 0.3659 13.7% 0.48 [0.41, 1.72] Test for overall effect: $Z = 0.63$ ($P = 0.53$) Total (85% CI) -100.0% 1.67 [1.12, 2.48] Heterogeneity: Tau ² = 0.17; Ch ² = 15.20, df = 6 ($P = 0.02$); $P = 61\%$ Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for subaroup differences: Ch ² = 0.18, df = 1 ($P = 0.67$), $P = 0\%$ Study or Subgroup log[Odds Ratio] SE Weight IV. Fixed, 95% CI 1.2.3 female non-fatal CV event Jimenez MC [35] 0.3646 0.2231 4.6% 1.44 [0.93, 2.23] John H.Page [27] 0.4574 0.1894 6.4% 1.58 [1.09, 2.29] Subtotal (85% CI) -111.0% 1.52 [1.15, 2.02] Heterogeneity: Ch ² = 0.10, df = 1 ($P = 0.75$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.004$) 1.2.4 male ACM Anna C Phillips (13] 0.555 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohisson (28) 0.3221 0.2533 3.6% 1.38 [0.24, 2.27] Paola Fordi [33] 0.1398 0.2282 2.9% 1.78 [1.40, 1.79] Heterogeneity: Ch ² = 0.33, df = 4 ($P = 0.47$); $P = 0\%$ Test for overall effect: $Z = 7.52$ ($P < 0.00001$) 1.2.5 male fatal CVevent Anna C Phillips (13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohisson (28] 0.4762 0.282 2.9% 1.78 [1.40, 1.79] Heterogeneity: Ch ² = 0.33, df = 4 ($P = 0.48$; $P = 0\%$ Test for overall effect: $Z = 7.52$ ($P < 0.00001$) 1.2.5 male fatal CVevent Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohisson (28] 0.6152 0.289 2.7% 1.85 [1.45, 1.75] Heterogeneity: Ch ² = 0.21, df = 2 ($P = 0.96$); $P = 0\%$ Test for overall effect: $Z = 3.72 (P = 0.0002)$ Total (95% CI) -0.01, 100.0% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 0.21, df = 2 ($P = 0.96$	ChrisandraShufelt [29]	0.8879	0.4233	11.9%	2.43 [1.06, 5.57]	
Subtotal (95% CI) 25.6% 1.40 [0.46, 3.96] Heterogeneity: Tau" = 0.41; Chi ² = 3.60, df = 1 ($P = 0.06$); $P = 72\%$ Test for overall effect: $Z = 0.63$ ($P = 0.53$) Total (95% CI) 100.0% 1.67 [1.12, 2.48] Heterogeneity: Tau" = 0.17; Chi ² = 15.20, df = 6 ($P = 0.02$); $P = 61\%$ Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for overall effect: $Z = 2.53$ ($P = 0.01$) Test for overall effect: $Z = 2.50$ ($P = 0.75$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.75$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.75$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.02$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.02$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.02$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.02$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.025$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.025$); $P = 0\%$ Test for overall effect: $Z = 2.90$ ($P = 0.025$); $P = 0\%$ Test for overall effect: $Z = 7.52$ ($P = 0.0001$) 1.2.5 male fatal CVevent Anna C Phillips (13] 0.48 ($P = 0.47$); $P = 0\%$ Test for overall effect: $Z = 7.52$ ($P = 0.0001$) 1.2.5 male fatal CVevent Anna C Phillips (13] 0.48 ($P = 0.47$); $P = 0\%$ Test for overall effect: $Z = 4.09$ ($P = 0.047$); $P = 0\%$ Test for overall effect: $Z = 4.09$ ($P = 0.047$); $P = 0\%$ Test for overall effect: $Z = 7.52$ ($P = 0.0001$) 1.2.5 male fatal CVevent Anna C Phillips (13] 0.48 ($P = 0.47$); $P = 0\%$ Test for overall effect: $Z = 0.234$, $df = 2$ ($P = 0.93$); $P = 0\%$ Test for overall effect: $Z = 4.09$ ($P = 0.0002$) Total (9% CI) 0.00% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 0.24, $df = 2$ ($P = 0.96$); $P = 0\%$ Test for overall effect: $Z = 0.73$ ($P = 0.0002$) Total (9% CI) 0.00% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 0.	D.P.Trivedi [31]	-0.1744	0.3659	13.7%	0.84 [0.41, 1.72]	
Heterogeneity: Tau ² = 0.41; Ch ² = 3.60, df = 1 (P = 0.06); P = 72% Test for overall effect: Z = 0.63 (P = 0.3) Total (95% CI) 100.0% 1.67 [1.12, 2.48] Heterogeneity: Tau ² = 0.17; Ch ² = 15.20, df = 6 (P = 0.02); P = 61% Test for overall effect: Z = 2.53 (P = 0.01) Test for overall effect: Z = 2.53 (P = 0.01) Test for overall effect: Z = 2.53 (P = 0.01) Test for overall effect: Z = 2.53 (P = 0.01) SE Weight IV, Fixed, 95% CI IV, Fixed, 95% CI 1.2.3 female non-fatal CV event Jimenez MC [35] 0.3646 0.2231 4.6% 1.44 [0.93, 2.23] John H-Page [27] 0.4574 0.1894 6.4% 1.58 [1.09, 2.29] Subtotal (95% CI) 11.0% 1.52 [1.15, 2.02] Heterogeneity: Ch ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.90 (P = 0.004) 1.2.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohlson [28] 0.3348 0.2234 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcelio Maggio [25] 0.3221 0.2533 3.6% 1.38 [1.40, 1.79] Heterogeneity: Ch ² = 0.33, df = 4 (P = 0.47); P = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.4678 0.288 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlson [28] 0.6152 0.289 2.7% 1.85 [1.40, 1.75] Heterogeneity: Ch ² = 0.34, df = 2 (P = 0.84); P = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.5 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlson [28] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlson [28] 0.6152 0.289 2.7% 1.85 [1.40, 1.273] Henry A, F [37] 0.678 0.2881 2.8% 1.97 [1.23, 3.46] Heterogeneity: Ch ² = 0.24, df = 2 (P = 0.80); P = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Total (95% CI) 100 (M = 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 0.24, df = 2 (P = 0.80); P = 0% Test for overall effect: Z = 9.73 (P	Subtotal (95% CI)			25.6%	1.40 [0.49, 3.96]	
Total (95% CI) 100.0% 1.67 [1.12, 2.48] Heterogeneity: Tau" = 0.17; Chi" = 15.20, df = 6 (P = 0.02); P = 61% Test for overall effect: Z = 2.52 (P = 0.01) Test for subaroup differences: Chi" = 0.18, df = 1 (P = 0.67), P = 0% Codds Ratio Odds	Heterogeneity: Tau ² = 0.4 Test for overall effect: Z =	1; Chi² = 3.60, df = 0.63 (P = 0.53)	1 (P = 0	0.06); l ² = 7	72%	
Heterogeneity: Tau ² = 0.17; Ch ² = 15.20, df = 6 (P = 0.02); P = 61% Test for overall effect: Z = 2.53 (P = 0.01) Test for suborou differences: Ch ² = 0.18, df = 1 (P = 0.67). P = 0% Odds Ratio Odds Ratio Odds Ratio Study or Subgroup log[Odds Ratio] SE Weight IV. Fixed .95% CI IV. Fixed .95% CI 1.2.3 female non-fatal CV event Jimenez MC [35] 0.3646 0.2231 4.6% 1.44 [0.93, 2.23] Subtotal (95% CI) 11.0% 1.52 [1.15, 2.02] Heterogeneity: Ch ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.90 (P = 0.004) 12.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohlsson [28] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.354 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Ch ² = 3.53, df = 4 (P = 0.47); P = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 1.75 [1.27, 1.95] Heterogeneity: Ch ² = 0.34, df = 2 (P = 0.84); P = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Heterogeneity: Ch ² = 0.21, df = 2 (P = 0.96); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 1000% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 500 100.0% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 500 100.0% 1.59 [1.	Total (95% CI)			100.0%	1.67 [1.12, 2.48]	◆
Test for overall effect: $Z = 2.53$ (P = 0.01) 0.01 0.1 1 10 100 Test for suboroup differences: Ch ² = 0.18. df = 1 (P = 0.67). P = 0%. 0.01 0.1 1 10 100 Favours experimental Favours control Subtration of the suboroup differences: Ch ² = 0.18. df = 1 (P = 0.67). P = 0%. Odds Ratio Odds Ratio Odds Ratio V. Fixed. 95% Cl IV. Fixed. 95% Cl	Heterogeneity: Tau ² = 0.1	7: Chi ² = 15.20, df	= 6 (P =	0.02): 12 =	61%	
Favours experimental Favours experimental Favours experimental Favours experimental Codds Ratio Odds Ratio Odds Ratio Study or Subgroup log(Odds Ratio) Study or Subgroup Odds Ratio Odds Ratio John H-Rage [27] 0.4574 0.18. df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.90 (P = 0.004) 1.2.4 male ACM Anna C Phillips [13] 0.455 0.816 34.4% 1.73 [1.48, 2.03] Class Colspan="2">Class Colspan="2"Class Colspa="2"Class Colspan="2"Class Colspan="2"Clas	Test for overall effect: Z =	2.53 (P = 0.01)	- (·			0.01 0.1 1 10 100
Odds Ratio Odds Ratio Odds Ratio Study or Subgroup log[Odds Ratio] SE Weight IV. Fixed, 95% CI IV. Fixed, 95% CI 1.2.3 female non-fatal CV event John H.Page [27] 0.4574 0.1894 6.4% 1.58 [1.09, 2.29] John H.Page [27] 0.4574 0.1894 6.4% 1.58 [1.09, 2.29] 1.10% Heterogeneity: Chi? = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.90 (P = 0.004) 1.52 [1.15, 2.02] Image: Chi? = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.90 (P = 0.004) 1.52 [1.05, 3.20] Image: Chi? = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 7.52 (P < 0.0001)	Test for subaroup differer	nces: Chi ² = 0.18. d	f = 1 (P	= 0.67). l²	= 0%	avours experimental Favours control
Study or Subgroup log[Odds Ratio] SE Weight N. Fixed, 95% CI IV. Fixed, 95% CI 1.2.3 female non-fatal CV event Jimenez MC [35] 0.3646 0.2231 4.6% 1.44 [0.93, 2.23] Jimenez MC [35] 0.3646 0.2231 4.6% 1.56 [1.09, 2.29] Subtotal (95% CI) 11.0% 1.52 [1.15, 2.02] Heterogeneity: Chi ² = 0.10, df = 1 (P = 0.75); P = 0% 1.52 [1.15, 2.02] Test for overall effect: Z = 2.90 (P = 0.004) 1.52 [1.15, 2.02] 1.2.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] O.P. Trivedi [31] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] 9.1 D.P. Trivedi [31] 0.3988 0.2232 2.9% 1.15 [0.66, 2.00] 9.1 Marcello Maggio [25] 0.3221 0.2533 3.6% 1.49 [1.11, 2.01] 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); P = 0% 1.58 [1.40, 1.79] 1.58 [1.40, 1.79] 1.58 [1.40, 1.79] I.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.452 1.28 [1.17, 1.95] 1.58 [1.05, 3.26] 1.57 [1.27, 1.95] 1.57 [1.27, 1.95] 1.5					Odds Ratio	Odds Ratio
1.2.3 female non-fatal CV event 1.44 [0.93, 2.23] John H.Page [27] 0.4574 0.1894 6.4% 1.58 [1.09, 2.29] Subtotal [95% C1] 11.0% 1.52 [1.15, 2.02] Heterogeneity: Chi ² = 0.10, df = 1 (P = 0.75); l ² = 0% 1.52 [1.15, 2.02] Test for overall effect: Z = 2.90 (P = 0.004) 1.52 [1.15, 2.02] 1.2.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohisson [28] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% C1) 61.2% 1.58 [1.40, 1.79] 1.58 [1.40, 1.79] 1.58 [1.40, 1.79] 1.58 [1.40, 1.79] 1.55 [0.00] 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] 1.57 [1.27, 1.95] 1.57 [1.27, 1.95] 1.57 [1.27, 1.95] 1.57 [1.27, 1.95] 1.57 [1.27, 1.95] 1.66 [1.01, 2.73] 1.66 [1.01, 2.73] 1.66 [1.01, 2.73] 1.66 [1.01, 2.73] 1.66 [1	Study or Subaroup	log[Odds Ratio]	SE	Weight	IV, Fixed. 95% CI	IV, Fixed, 95% CI
Jimenez MC [35] 0.3646 0.2231 4.6% 1.44 [0.93, 2.23] John H.Page [27] 0.4574 0.1894 6.4% 1.58 [1.09, 2.29] Subtotal (95% CI) 11.0% 1.52 [1.15, 2.02] Heterogeneity: Ch ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.90 (P = 0.004) 1.2.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohlsson [28] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Ch ² = 3.53, df = 4 (P = 0.47); P = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.57 [1.27, 1.95] Heterogeneity: Ch ² = 0.34, df = 2 (P = 0.84); P = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2533 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% CI) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Ch ² = 0.21, df = 2 (P = 0.96); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 3.72 (P < 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 9.73 (P < 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Ch ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 9.73 (P < 0.0002) Total (95% CI) 10.1 1 10 100 Favours experimental Favours control	1.2.3 female non-fatal (CV event				
$\begin{array}{c} \text{Interms 1} \text{ for } (5) & \text{Out} (5$	limenez MC [35]	0.3646	0 2231	4 6%	1 44 [0 93 2 23]	-
Subtotal (95% Cl) 11.0% 1.52 [1.15, 2.02] Heterogeneity: Chi ² = 0.10, df = 1 (P = 0.75); I ² = 0% Test for overall effect: Z = 2.90 (P = 0.004) 12.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohlsson [28] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% Cl) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); I ² = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anton Ponholzer [38] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% Cl) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); I ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); I ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 0.76 (P < 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Favours experimental Favours control	John H.Page [27]	0.4574	0.1894	6.4%	1.58 [1.09, 2.29]	
Heterogeneity: Chi ² = 0.10, df = 1 (P = 0.75); P = 0% Test for overall effect: Z = 2.90 (P = 0.004) 1.2.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohlsson [28] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% Cl) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); P = 0% Test for overall effect: Z = 7.52 (P < 0.0001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% Cl) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); P = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.87 [1.37, 1.95] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 10.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subroun differences: Chi ² = 0.76 off = 3 (P = 0.86); P = 0% Test for overall effect: Z = 0.76 (P < 0.0001) Favours experimental Favours control	Subtotal (95% CI)	0.4014	0.1001	11.0%	1.52 [1.15, 2.02]	◆
Total opportunity is a first for overall effect: $Z = 2.90 (P = 0.004)$ 1.2.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohlsson [28] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); P = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); P = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% CI) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronu differences: Chi ² = 0.76 (f = 3 (P = 0.66)) P = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronu offerences: Chi ² = 0.76 (f = 3 (P = 0.66)) P = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronu offerences: Chi ² = 0.76 (f = 3 (P = 0.66)) P = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronu offerences: Chi ² = 0.76 (f = 3 (P = 0.66)) P = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronu offerences: Chi ² = 0.76 (f = 3 (P = 0.66)) P = 0%	Heterogeneity: $Chi^2 = 0$	10 df = $1 (P = 0.7)$	5): $I^2 = 0$	%		
1.2.4 male ACM Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohlsson [28] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); P ² = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); P ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% CI) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); P ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); P ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.96); P ² = 0% Test for overall effect: Z = 9.73 (P < 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 0.73 (P < 0.00001) Test for subronu differences: Chi ² = 0.76 df = 3 (P = 0.66) P ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronu differences: Chi ² = 0.76 df = 3 (P = 0.66) P ² = 0% Favours experimental Favours control	Test for overall effect: Z	= 2.90 (P = 0.004)),			
Anna C Phillips [13] 0.55 0.0816 34.4% 1.73 [1.48, 2.03] Claes Ohisson [28] 0.3988 0.1224 15.1% 1.49 [1.17, 1.90] D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.54, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); P ² = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohisson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); P ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohisson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% CI) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); P ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); P ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); P ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronu differences: Chi ² = 0.76 df = 3 (P = 0.66) P ² = 0% Favours experimental Favours control	1.2.4 male ACM					
Claes Ohisson [28] 0.3988 0.1234 15.1% 1.49 [1.17, 1.90] D.P. Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% Cl) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); I ² = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohisson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P. Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% Cl) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); I ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohisson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); I ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subround differences: Chi ² = 0.76 df = 3 (P = 0.66) I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subround differences: Chi ² = 0.76 df = 3 (P = 0.66) I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subround differences: Chi ² = 0.76 df = 3 (P = 0.66) I ² = 0% Favours experimental Favours control	Anna C Phillips [13]	0.55	0.0816	34.4%	1.73 [1.48, 2.03]	
D.P.Trivedi [31] 0.3148 0.2087 5.3% 1.37 [0.91, 2.06] Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); I ² = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohisson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); I ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohisson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A, F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% CI) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); I ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Favours experimental Favours control	Claes Ohlsson [28]	0.3988	0.1234	15.1%	1.49 [1.17, 1.90]	•
Marcello Maggio [25] 0.3221 0.2533 3.6% 1.38 [0.84, 2.27] Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); l ² = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); l ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% CI) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); l ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronu differences: Chi ² = 0.76 df = 3 (P = 0.66) l ² = 0% Favours experimental Favours control	D.P.Trivedi [31]	0.3148	0.2087	5.3%	1.37 [0.91, 2.06]	
Paola Forti [33] 0.1398 0.2823 2.9% 1.15 [0.66, 2.00] Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); l ² = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CV event Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); l ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% CI) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for suboroun differences: Chi ² = 0.76 df = 3 (P = 0.66) l ² = 0% Favours experimental Favours control	Marcello Maggio [25]	0.3221	0.2533	3.6%	1.38 [0.84, 2.27]	
Subtotal (95% CI) 61.2% 1.58 [1.40, 1.79] Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); P = 0% Test for overall effect: Z = 7.52 (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P. Trived [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% CI) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); P = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% CI) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); P = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); P = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subronup differences: Chi ² = 0.76 df = 3 (P = 0.86) ² = 0% Favours experimental Favours control	Paola Forti [33]	0.1398	0.2823	2.9%	1.15 [0.66, 2.00]	
Heterogeneity: Chi ² = 3.53, df = 4 (P = 0.47); ² = 0% Test for overall effect: $Z = 7.52$ (P < 0.00001) 1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% Cl) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); ² = 0% Test for overall effect: $Z = 4.09$ (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); ² = 0% Test for overall effect: $Z = 3.72$ (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); ² = 0% Test for overall effect: $Z = 9.73$ (P < 0.00001) Test for subornu differences: Chi ² = 0.76 df = 3 (P = 0.66) ² = 0% Favours experimental Favours control	Subtotal (95% CI)			61.2%	1.58 [1.40, 1.79]	•
1.2.5 male fatal CVevent Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P. Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% Cl) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); l ² = 0% 1.87 [1.27, 1.95] Test for overall effect: Z = 4.09 (P < 0.0001)	Heterogeneity: Chi ² = 3. Test for overall effect: Z	53, df = 4 (P = 0.4 = 7.52 (P < 0.000	7); l² = 0 01)	%		
Anna C Phillips [13] 0.4 0.1531 9.8% 1.49 [1.11, 2.01] Claes Ohlsson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% Cl) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); $P^2 = 0\%$ Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); $P^2 = 0\%$ Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); $P^2 = 0\%$ Test for overall effect: Z = 9.73 (P < 0.00001) Test for subornup differences: Chi ² = 0.76 df = 3 (P = 0.86) P = 0\%	1.2.5 male fatal CVever	nt				
Claes Ohisson [28] 0.4762 0.1944 6.1% 1.61 [1.10, 2.36] D.P.Trivedi [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% Cl) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); l ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohisson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); l ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for overall effect: Z = 9.73 (P < 0.00001) Test for overall effect: Z = 9.76 df = 3 (P = 0.66) l ² = 0% Favours experimental Favours control	Anna C Phillips [13]	0.4	0.1531	9.8%	1.49 [1.11.2.01]	-
D.P. Trived [31] 0.5822 0.282 2.9% 1.79 [1.03, 3.11] Subtotal (95% Cl) 18.7% 1.57 [1.27, 1.95] Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); I ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); I ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subround differences: Chi ² = 0.76 df = 3 (P = 0.86) I ² = 0% Favours experimental Favours control	Claes Ohlsson [28]	0.4762	0.1944	6.1%	1.61 [1.10, 2.36]	
Subtotal (95% Cl) Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); I ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohisson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); I ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subornun differences: Chi ² = 0.76 df = 3 (P = 0.86) I ² = 0% Favours experimental Favours control	D.P.Trivedi [31]	0.5822	0.282	2.9%	1.79 [1.03 3.11]	
Heterogeneity: Chi ² = 0.34, df = 2 (P = 0.84); I ² = 0% Test for overall effect: Z = 4.09 (P < 0.0001) 1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); I ² = 0% Test for overall effect: Z = 3.72 (P = 0.002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subornup differences: Chi ² = 0.76 df = 3 (P = 0.86) I ² = 0% Favours experimental Favours control	Subtotal (95% CI)	0.0022	0.202	18.7%	1.57 [1.27, 1.95]	♦
1.2.6 male non-fatal CV event Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohisson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21 , df = 2 (P = 0.90); l ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94 , df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for overall effect: Z = 9.76 (ff = 3 (P = 0.66) l ² = 0% Favours experimental Favours control	Heterogeneity: Chi ² = 0. Test for overall effect: Z	34, df = 2 (P = 0.8 = 4.09 (P < 0.000	4); I² = 0 1)	%		
Anton Ponholzer [38] 0.6152 0.289 2.7% 1.85 [1.05, 3.26] Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); l ² = 0% Test for overall effect: Z = 3.72 (P = 0.002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for suborrup differences: Chi ² = 0.76 df = 3 (P = 0.66) l ² = 0% Favours experimental Favours control	1.2.6 male non-fatal CV	/ event				
Claes Ohlsson [28] 0.5068 0.2535 3.6% 1.66 [1.01, 2.73] Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); l ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subornup differences: Chi ² = 0.76 df = 3 (P = 0.86) l ² = 0% Favours experimental Favours control	Anton Ponholzer [38]	0.6152	0.289	2.7%	1.85 [1.05, 3.26]	
Henry A. F [37] 0.678 0.2881 2.8% 1.97 [1.12, 3.46] Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); l ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for suborrup differences: Chi ² = 0.76 df = 3 (P = 0.66) l ² = 0% Favours experimental Favours control	Claes Ohlsson [28]	0.5068	0.2535	3.6%	1.66 [1.01, 2.73]	
Subtotal (95% Cl) 9.1% 1.81 [1.32, 2.47] Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); I ² = 0% 7est for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); I ² = 0% 0.01 0.1 Test for overall effect: Z = 9.73 (P < 0.00001)	Henry A. F [37]	0.678	0.2881	2.8%	1.97 [1.12. 3.46]	
Heterogeneity: Chi ² = 0.21, df = 2 (P = 0.90); l ² = 0% Test for overall effect: Z = 3.72 (P = 0.0002) Total (95% Cl) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.0001) Test for suborrup differences: Chi ² = 0.76, df = 3 (P = 0.66), l ² = 0% Favours experimental Favours control	Subtotal (95% CI)			9.1%	1.81 [1.32, 2.47]	•
Total (95% CI) 100.0% 1.59 [1.45, 1.75] Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% 0.01 0.1 1 10 100 Test for overall effect: Z = 9.73 (P < 0.00001)	Heterogeneity: Chi ² = 0 Test for overall effect: Z	21, df = 2 (P = 0.9 = 3.72 (P = 0.000)	0); I² = 0 2)	%	con 6 - -	
Heterogeneity: Chi ² = 4.94, df = 12 (P = 0.96); l ² = 0% Test for overall effect: Z = 9.73 (P < 0.00001) Test for subaroun differences: Chi ² = 0.76, df = 3 (P = 0.86), l ² = 0% Favours experimental Favours control	Total (95% CI)			100.0%	1.59 [1.45. 1.75]	•
Test for overall effect: $Z = 9.73$ (P < 0.00001) Test for subaround differences: Chi ² = 0.76 df = 3 (P = 0.86) l ² = 0%	Heterogeneity: $Chi^2 = 4$	94. df = 12 (P = 0	96): l ² =	0%		
Test for subgroup differences: Chi ² = 0.76, df = 3 (P = 0.86) l ² = 0%	Test for overall effect: 7	= 9.73 (P < 0.000	01)	0,0		0.01 0.1 1 10 100
	Test for subgroup differe	ances: Chi ² = 0.76	df = 3.0	P = 0.86	I ² = 0%	avours experimental Favours control

Figure 5. Subgroup analysis of the relationship between dehydroepiandrosterone sulfate and prognosis of cardiovascular (CV) disease. ACM indicates all-cause mortality.

Subgroup Analysis

To explore possible sources of heterogeneity among the eligible studies, subgroup analysis was performed. As shown in Tables 3 through 5, different set of variables seemed to have no apparent effect on pooled HRs. At the same time, we performed subgroup analysis according to sex (see Figure 5).

Publication Bias

The funnel plot (Figure 6) for studies of DHEAS and ACM and fatal and nonfatal cardiovascular events shows reasonable symmetry at the top of the funnel plot and slight asymmetry at the bottom, suggesting some evidence of publication bias for small studies.

Discussion

In this meta-analysis, we found that CVD patients with lower DHEAS levels may have poorer prognosis than those with higher DHEAS levels. To the best of our knowledge, this is the first systematic review and meta-analysis to clarify the relationship between DHEAS and CVD outcomes.

Our meta-analysis included all English-language and Chinese-language published studies up until September 5, 2016, that compared CVD outcomes in patients with lower or higher concentration of DHEAS. Twenty-five published studies were selected according to specified inclusion criteria, for a total of 92 489 patients. Of note, a lower concentration of DHEAS was associated with a significantly increased risk of overall mortality when all studies were considered (risk ratio, 1.47; 95% Cl, 1.38–1.56).

Sex hormones play a pivotal role in regulating body composition both in men and women. DHEAS as their precursor has been shown to have many biological effects, and the clinical significance of DHEA and DHEAS in CVD remains uncertain. Epidemiological studies demonstrate that the association between low DHEAS and all-cause disease or CVD mortality is conflicting. Most of the studies in men show a negative relationship between DHEAS level and mortality and CVD mobility.^{20,30,31,36,39,47,48} Similar conclusions in postmenopausal women with low DHEAS levels have been reported and are associated with higher cardiovascular





Downloaded from http://ahajournals.org by on October 30, 2024

mortality.^{27,29} Conversely, no association was observed between DHEAS and mortality in several studies.^{49–51} Our meta-analysis including 92 489 patients clarified the relationship between DHEAS and CVD prognosis, which indicated the adrenal androgen DHEA and its sulfate form DHEAS, may be markers of the aging process and potential longevity.⁵²

Much evidence has indicated that obesity, type 2 diabetes mellitus, and the metabolic syndrome in men are all characterized by a hypogonadotropic hypogonadism, strictly related to body fat mass.^{53–56} Corona et al⁵⁷ reported that DHEA supplementation was associated with a reduction of fat mass and a trend toward an increase in lean mass. Although these effects were small and can be accounted for by adjustment for DHEA-derived metabolites, it provides a new train of thought to prevent the occurrence of CVD and reduce the long-term risk of death.

The mechanisms of the effect of DHEA and DHEAS on health outcomes remain unclear. Although DHEAS does not directly interact with the glucocorticoid receptor, research suggests that it may act as a functional antagonist to the effects of glucocorticoids.⁵⁸⁻⁶⁰ This counterbalancing action might explain the relationship between DHEAS level and health outcomes known to be affected by chronically elevated cortisol levels, such as heart disease, diabetes mellitus, and cognitive impairment.^{61,62} A direct role for DHEA in opposing atherosclerosis is suggested by its ability to facilitate fibrinolysis, 63,64 inhibit platelet aggregation, and retard cell proliferation.⁶⁵ Previous pathological research elucidated that the zona reticularis, which is responsible for DHEA production, is highly susceptibility to vascular damage.⁶⁶ Given these findings, DHEAS might reflect underlying vascular disease manifesting as endocrine dysfunction.

Study Limitations

Limitations of the present meta-analysis are essentially associated with the overall weakness of the studies reviewed, including the small size of the studies, the low statistical power, the often unreliable analytical methods for steroid detection, the different evaluation of confounding factors in the different studies such as sex, age, smoking, diabetes mellitus, metabolic syndrome, hypertension, obesity, dyslipidemia, and thyroid disease; the variation of aldosterone values; the treatments with corticosteroids or hypertension or menopause in women; the use of aldosteronereceptor blockers, different kinds of diuretics and other drugs that affect DHEAS level. At last, the differences in the clinical end points or populations analyzed. There is still a lack of basic understanding of the biological effects of DHEA and DHEAS and further data in men and in women from prospective studies including better assessment of covariates, and randomized trials are urgently needed.

Conclusions

The results of the present meta-analysis indicate that DHEAS is a poor prognostic marker for patients with CVD. Further studies are needed to uncover the potential mechanisms between low DHEAS level and poor prognosis in CVD patients.

Sources of Funding

This work was supported financially by the National Natural Science Foundation of China (81560070).

Disclosures

None.

References

- Regelson W, Kalimi M. Dehydroepiandrosterone (DHEA)—the multifunctional steroid. II. Effects on the CNS, cell proliferation, metabolic and vascular, clinical and other effects. Mechanism of action? *Ann N Y Acad Sci.* 1994;719:564–575.
- 2. Labrie F. Intracrinology. Mol Cell Endocrinol. 1991;78:C113-C118.
- Zwain IH, Yen SS. Dehydroepiandrosterone: biosynthesis and metabolism in the brain. *Endocrinology*. 1999;140:880–887.
- Cox JL, Chang Y, Ramaraj P. In-vitro determination of biological and anabolic functions of weak androgen dehydroepiandrosterone (DHEA) using a variety of cell lines. *Open J Endocr Metab Dis.* 2015;5:105–116.
- Labrie F. DHEA, important source of sex steroids in men and even more in women. Prog Brain Res. 2010;182:97–148.
- Saczawa ME, Graber JA, Brooks-Gunn J, Warren MP. Methodological considerations in use of the cortisol/DHEA(S) ratio in adolescent populations. *Psychoneuroendocrinology*. 2013;38:2815–2819.
- de Bruin VM, Vieira MC, Rocha MN, Viana GS. Cortisol and dehydroepiandosterone sulfate plasma levels and their relationship to aging, cognitive function, and dementia. *Brain Cogn.* 2002;50:316–323.
- Phillips AC, Carroll D, Gale CR, Lord JM, Arlt W, Batty GD. Cortisol, DHEAS, their ratio and the metabolic syndrome: evidence from the Vietnam Experience Study. *Eur J Endocrinol.* 2010;162:919–923.
- Vuksan-Ćusa B, Sagud M, Mihaljević-Peleš A, Jakšić N, Jakovljević M. Metabolic syndrome and cortisol/DHEAS ratio in patients with bipolar disorder and schizophrenia. *Psychiatr Danub*. 2014;26:187–189.
- Mora M, Serra-Prat M, Palomera E, Puig-Domingo M. Metabolic and hormonal contributors to survival in the participants of the Mataro Ageing Study at 8 years follow-up. *Clin Endocrinol (Oxf)*. 2014;81:775–783.
- Boscarino JA. A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: implications for surveillance and prevention. *Psychosom Med.* 2008;70:668–676.
- Blum CA, Mueller C, Schuetz P, Fluri F, Trummler M, Mueller B, Katan M, Christ-Crain M. Prognostic value of dehydroepiandrosterone-sulfate and other parameters of adrenal function in acute ischemic stroke. *PLoS One*. 2013;8: e63224.
- Phillips AC, Carroll D, Gale CR, Lord JM, Arlt W, Batty GD. Cortisol, DHEA sulphate, their ratio, and all-cause and cause-specific mortality in the Vietnam Experience Study. *Eur J Endocrinol.* 2010;163:285–292.
- Butcher SK, Killampalli V, Lascelles D, Wang K, Alpar EK, Lord JM. Raised cortisol:DHEAS ratios in the elderly after injury: potential impact upon neutrophil function and immunity. *Aging Cell*. 2005;4:319–324.
- Maggi M, Buvat J, Corona G, Guay A, Torres LO. Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA). J Sex Med. 2013;10:661– 677.
- Traish AM, Kang HP, Saad F, Guay AT. Dehydroepiandrosterone (DHEA): a precursor steroid or an active hormone in human physiology. J Sex Med. 2011;8:2960–2982; quiz 2983.
- Labrie F. DHEA, important source of sex steroids in men and even more in women. Prog Brain Res. 2010;182:97–148.

- Araujo AB, Wittert GA. Endocrinology of the aging male. Best Pract Res Clin Endocrinol Metab. 2011;25:303–319.
- Kushnir MM, Blamires T, Rockwood AL, Roberts WL, Yue B, Erdogan E, Bunker AM, Meikle AW. Liquid chromatography-tandem mass spectrometry assay for androstenedione, dehydroepiandrosterone, and testosterone with pediatric and adult reference intervals. *Clin Chem.* 2010;56:1138–1147.
- Barrett-Connor E, Khaw KT, Yen SS. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. N Engl J Med. 1986; 315:1519–1524.
- Słowinska-Srzednicka J, Zgliczyński S, Ciświcka-Sznajderman M, Srzednicki M, Soszyński P, Biernacka M, Woroszyłska M, Ruzyłło W, Sadowski Z. Decreased plasma dehydroepiandrosterone sulfate and dehydroepiandrosterone concentrations in young men after myocardial infarction. *Atherosclerosis*. 1989; 79:197–203.
- Mitchell LE, Sprecher DL, Borecki IB, Rice T, Laskarzewski PM, Rao DC. Evidence for an association between dehydroepiandrosterone sulfate and nonfatal, premature myocardial infarction in males. *Circulation*. 1994;89:89– 93.
- Słowińska-Srzednicka J, Malczewska B, Srzednicki M, Chotkowska E, Brzezińska A, Zgliczyński W, Ossowski M, Jeske W, Zgliczyński S, Sadowski Z. Hyperinsulinaemia and decreased plasma levels of dehydroepiandrosterone sulfate in premenopausal women with coronary heart disease. *J Intern Med*. 1995;237:465–472.
- Barrett-Connor E, Goodman-Gruen D. Dehydroepiandrosterone sulfate does not predict cardiovascular death in postmenopausal women: the Rancho Bernardo Study. *Circulation*. 1995;91:1757–1760.
- Maggio M, Lauretani F, Ceda GP, Bandinelli S, Ling SM, Metter EJ, Artoni A, Carassale L, Cazzato A, Ceresini G, Guralnik JM, Basaria S, Valenti G, Ferrucci L. Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti Area (Inchianti) study. *Arch Intern Med*. 2007;167:2249–2254.
- Cappola AR, Xu QL, Walston JD, Leng SX, Ferrucci L, Guralnik J, Fried LP. DHEAS levels and mortality in disabled older women: the Women's Health and Aging Study I. J Gerontol A Biol Sci Med Sci. 2006;61:957–962.
- Page JH, Ma J, Rexrode KM, Rifai N, Manson JE, Hankinson SE. Plasma dehydroepiandrosterone and risk of myocardial infarction in women. *Clin Chem.* 2008;54:1190–1196.
- Ohlsson C, Labrie F, Barrett-Connor E, Karlsson MK, Ljunggren O, Vandenput L, Mellström D, Tivesten A. Low serum levels of dehydroepiandrosterone sulfate predict all-cause and cardiovascular mortality in elderly Swedish men. J *Clin Endocrinol Metab.* 2010;95:4406–4414.
- 29. Shufelt C, Bretsky P, Almeida CM, Johnson BD, Shaw LJ, Azziz R, Braunstein GD, Pepine CJ, Bittner V, Vido DA, Stanczyk FZ, Bairey Merz CN. DHEA-S levels and cardiovascular disease mortality in postmenopausal women: results from the National Institutes of Health-National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE). J Clin Endocrinol Metab. 2010;95:4985–4992.
- Hsu HJ, Yen CH, Chen CK, Hsu KH, Hsiao CC, Lee CC, Wu IW, Sun CY, Chou CC, Hsieh MF, Chen CY, Hsu CY, Tsai CJ, Wu MS. Low plasma DHEA-S increases mortality risk among male hemodialysis patients. *Exp Gerontol.* 2012;47:950–957.
- Trivedi DP, Khaw KT. Dehydroepiandrosterone sulfate and mortality in elderly men and women. J Clin Endocrinol Metab. 2001;86:4171–4177.
- Jansson JH, Nilsson TK, Johnson O. von Willebrand factor, tissue plasminogen activator, and dehydroepiandrosterone sulphate predict cardiovascular death in a 10 year follow up of survivors of acute myocardial infarction. *Heart*. 1998;80:334–337.
- Forti P, Maltoni B, Olivelli V, Pirazzoli GL, Ravaglia G, Zoli M. Serum dehydroepiandrosterone sulfate and adverse health outcomes in older men and women. *Rejuvenation Res.* 2012;15:349–358.
- 34. Jankowska EA, Drohomirecka A, Ponikowska B, Witkowska A, Lopuszanska M, Szklarska A, Borodulin-Nadzieja L, Banasiak W, Poole-Wilson PA, Ponikowski P. Deficiencies in circulating testosterone and dehydroepiandrosterone sulphate, and depression in men with systolic chronic heart failure. *Eur J Heart Fail.* 2010;12:966–973.
- Jiménez MC, Sun Q, Schürks M, Chiuve S, Hu FB, Manson JE, Rexrode KM. Low dehydroepiandrosterone sulfate is associated with increased risk of ischemic stroke among women. *Stroke*. 2011;44:1784–1789.
- 36. Sanders JL, Boudreau RM, Cappola AR, Arnold AM, Robbins J, Cushman M, Newman AB. Cardiovascular disease is associated with greater incident dehydroepiandrosterone sulfate decline in the oldest old: the Cardiovascular Health Study All Stars Study. J Am Geriatr Soc. 2010;58:421–426.
- Feldman HA, Johannes CB, Araujo AB, Mohr BA, Longcope C, McKinlay JB. Low dehydroepiandrosterone and ischemic heart disease in middle-aged men:

prospective results from the Massachusetts Male Aging Study. *Am J Epidemiol*. 2001;153:79–89.

- Ponholzer A, Madersbacher S, Rauchenwald M, Jungwirth S, Fischer P, Tragl KH. Vascular risk factors and their association to serum androgen levels in a population-based cohort of 75-year-old men over 5 years: results of the VITA study. *World J Urol.* 2009;28:209–214.
- Glei DA, Goldman N. Dehydroepiandrosterone sulfate (DHEAS) and risk for mortality among older Taiwanese. Ann Epidemiol. 2006;16:510–515.
- Fukai S, Akishita M, Yamada S, Ogawa S, Yamaguchi K, Kozaki K, Toba K, Ouchi Y. Plasma sex hormone levels and mortality in disabled older men and women. *Geriatr Gerontol Int.* 2011;11:196–203.
- Arnlöv J, Pencina MJ, Amin S, Nam BH, Benjamin EJ, Murabito JM, Wang TJ, Knapp PE, D'Agostino RB Sr, Bhasin S, Vasan RS. Endogenous sex hormones and cardiovascular disease incidence in men. *Ann Intern Med*. 2006;145:176–184.
- Tivesten Å, Vandenput L, Carlzon D, Nilsson M, Karlsson MK, Ljunggren Ö, Barrett-Connor E, Mellström D, Ohlsson C. Dehydroepiandrosterone and its sulfate predict the 5-year risk of coronary heart disease events in elderly men. J Am Coll Cardiol. 2014;64:1801–1810.
- Güder G, Frantz S, Bauersachs J, Allolio B, Ertl G, Angermann CE, Störk S. Low circulating androgens and mortality risk in heart failure. *Heart*. 2009;95:504– 509.
- 44. Barrett-Connor E, Goodman-Gruen D. The epidemiology of DHEAS and cardiovascular disease. *Ann N Y Acad Sci.* 1995;774:259–270.
- LaCroix AZ, Yano K, Reed DM. Dehydroepiandrosterone sulfate, incidence of myocardial infarction, and extent of atherosclerosis in men. *Circulation*. 1992;86:1529–1535.
- 46. Haring R, Teng Z, Xanthakis V, Coviello A, Sullivan L, Bhasin S, Murabito JM, Wallaschofski H, Vasan RS. Association of sex steroids, gonadotrophins, and their trajectories with clinical cardiovascular disease and all-cause mortality in elderly men from the Framingham Heart Study. *Clin Endocrinol (Oxf)*. 2013;78:629–634.
- Cappola AR, O'Meara ES, Guo W, Bartz TM, Fried LP, Newman AB. Trajectories of dehydroepiandrosterone sulfate predict mortality in older adults: the Cardiovascular Health Study. J Gerontol A Biol Sci Med Sci. 2009;64:1268– 1274.
- Berr C, Lafont S, Debuire B, Dartigues JF, Baulieau EE. Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: a French community based study. *Proc Natl Acad Sci USA*. 1996;93:13410–13415.
- Legrain S, Berr C, Frenoy N, Gourlet V, Debuire B, Baulieu EE. Dehydroepiandrosterone sulfate in a long-term care aged population. *Gerontology*. 1995;41:343–351.
- Tilvis RS, Kähönen M, Härkönen M. Dehydroepiandrosterone sulfate, diseases and mortality in a general aged population. *Aging (Milano)*. 1999;11:30–34.
- Kähönen MH, Tilvis RS, Jolkkonen J, Pitkälä K, Härkönen M. Predictors and clinical significance of declining plasma dehydroepiandrosterone sulfate in old age. *Aging (Milano)*. 2000;12:308–314.
- Yen SS. Dehydroepiand rosterone sulfate and longevity: new clues for an old friend. *Proc Natl Acad Sci USA*. 2001;98:8167–8169.
- Corona G, Rastrelli G, Morelli A, Vignozzi L, Mannucci E, Maggi M. Hypogonadism and metabolic syndrome. J Endocrinol Invest. 2011;34:557–567.
- Corona G, Mannucci E, Forti G, Maggi M. Following the common association between testosterone deficiency and diabetes mellitus, can testosterone be regarded as a new therapy for diabetes? *Int J Androl.* 2009;32:431–441.
- Corona G, Rastrelli G, Vignozzi L, Mannucci E, Maggi M. Testosterone, cardiovascular disease and the metabolic syndrome. *Best Pract Res Clin Endocrinol Metab.* 2011;25:337–353.
- Saad F, Aversa A, Isidori AM, Gooren LJ. Testosterone as potential effective therapy in treatment of obesity in men with testosterone deficiency: a review. *Curr Diabetes Rev.* 2012;8:131–143.
- Corona G, Rastrelli G, Giagulli VA, Sila A, Sforza A, Forti G, Mannucci E, Maggi M. Dehydroepiandrosterone supplementation in elderly men: a meta-analysis study of placebo-controlled trials. *J Clin Endocrinol Metab.* 2013;98:3615– 3626.
- Browne ES, Porter JR, Correa G, Abadie J, Svec F. Dehydroepiandrosterone regulation of the hepatic glucocorticoid receptor in the Zucker rat. The obesity research program. J Steroid Biochem Mol Biol. 1993;45:517–524.
- Kalimi M, Shafagoj Y, Loria R, Padgett D, Regelson W. Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA). *Mol Cell Biochem.* 1994;131:99– 104.
- Wolf OT, Kirschbaum C. Actions of dehydroepiandrosterone and its sulfate in the central nervous system: effects on cognition and emotion in animals and humans. *Brain Res Rev.* 1999;30:264–298.

Downloaded from http://ahajournals.org by on October 30, 2024

DHEAS and CVD Wu et al

- Lupien SJ, Nair NP, Brière S, Maheu F, Tu MT, Lemay M, McEwen BS, Meaney MJ. Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. *Rev Neurosci.* 1999; 10:117–139.
- Vanitallie TB. Stress: a risk factor for serious illness. *Metabolism*. 2002;51:40– 45.
- Nilsson T, Mellbring G, Damber JE. Relationships between tissue plasminogen activator, steroid hormones, and deep vein thrombosis. *Acta Chir Scand*. 1985;151:515–519.
- 64. Beer NA, Jakubowicz DJ, Matt DW, Beer RM, Nestler JE. Dehydroepiandrosterone reduces plasma plasminogen activator inhibitor type 1 and tissue plasminogen activator antigen in men. *Am J Med Sci.* 1996;311:205–210.
- Gordon GB, Newitt JA, Shantz LM, Weng DE, Talalay P. Inhibition of the conversion of 3T3 fibroblast clones to adipocytes by dehydroepiandrosterone and related anticarcinogenic steroids. *Cancer Res.* 1986;46:3389–3395.
- Angeli A, Masera RG, Magri F, Ferrari E. The adrenal cortex in physiological and pathological aging: issues of clinical relevance. J Endocrinol Invest. 1999; 22:13–18.