

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

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**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

Dehydroepiandrosterone (DHEA) and its sulphated ester (DHEAS), working as multifunctional steroids,<sup>1</sup> are mainly produced in the adrenal cortex and converted to testosterone and estradiol in target tissues via androgen-converting enzymes.<sup>2</sup> DHEA is also synthesized in brain from 17OH pregnenolone and skin.<sup>3</sup> 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.<sup>4</sup> The concentrations of DHEAS are sex related

and vary during life.<sup>5</sup> 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,<sup>6</sup> Alzheimer's disease,<sup>7</sup> metabolic syndrome,<sup>8–10</sup> and all-cause mortality (ACM).<sup>10–13</sup> By far, the strongest associations with the metabolic syndrome were observed in the cortisol/DHEAS ratio by Phillips et al.<sup>8</sup> 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.<sup>14</sup>

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 age-related 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.<sup>15–19</sup> Special interest in the

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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).<sup>20–23</sup> These findings were not confirmed by a later study<sup>24</sup> 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

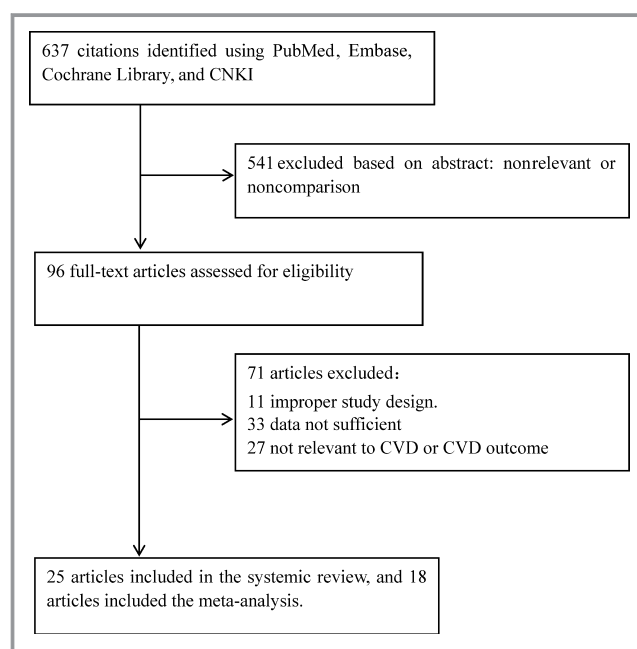
Data extraction and quality assessment were performed independently by 2 authors (T.-T.W. and Y.C.). The following data were extracted from eligible studies: names of the first authors, publication year, sources of participants, sample sizes, participants' characteristics, follow-up durations, end points 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:  $(\ln \text{upper limit} - \ln \text{HR}) / 1.96$ . 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 chi-square test with significance set at  $P < 0.10$ , and heterogeneity was quantified using the  $I^2$  statistic.  $I^2$  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 <sup>12</sup>	2013	United States	White	Prospective	231	71±14	59	1 y	6
Phillips et al <sup>13</sup>	2010	Vietnam	Asian	Retrospective	4255	38.3	100	15 y	8
Maggio et al <sup>25</sup>	2007	Italy	White	Retrospective	410	65–92	100	6 y	8
Cappola et al <sup>26</sup>	2006	United States	White	Prospective	539	77.6 (66–100)	0	5 y	7
Page et al <sup>27</sup>	2008	United States	White	Prospective	32 826	43–69	0	8–9 y	7
Ohlsson et al <sup>28</sup>	2010	Sweden	White	Prospective	2644	75.5±3.2	100	4.5 y	7
Shufelt et al <sup>29</sup>	2010	United States	White	Prospective	270	64±10	0	9 y	7
Hsu et al <sup>30</sup>	2012	Taiwan	Asian	Prospective	200	58.5±13.9	47	38.2 mo	7
Trivedi et al <sup>31</sup>	2001	United Kingdom	White	Prospective	963	65–76	100	6–10 y	7
Trivedi et al <sup>31</sup>	2001	United Kingdom	White	Prospective	1171	65–76	0	6–10 y	7
Jansson et al <sup>32</sup>	1998	Sweden	White	Prospective	123	≤70	77	10.5 y	7
Forti et al <sup>33</sup>	2012	Italy	White	Prospective	920	73.7±6.6	45	8 y	8
Jankowska et al <sup>34</sup>	2010	Poland	White	Prospective	163	60±10	100	28 mo	8
Jiménez et al <sup>35</sup>	2013	United States	White	Prospective	32 826	43–69	0	10 y	6
Sanders et al <sup>36</sup>	2010	United States	White	Retrospective	989	85.2	36.5	9 y	7
Feldman et al <sup>37</sup>	2001	United States	White	Prospective	1167	40–70	100	8.9 y	7
Ponholzer et al <sup>38</sup>	2009	Vienna	White	Prospective	247	75.8	100	5 y	7
Glei et al <sup>39</sup>	2006	Taiwan	Asian	Prospective	963	54–91	57.9	3 y	8
Fukai et al <sup>40</sup>	2011	Japan	Asian	Prospective	97	83±7	0	45 mo	8
Arnlov et al <sup>41</sup>	2006	United States	White	Prospective	1928	55±12	100	10 y	7
Tivesten et al <sup>42</sup>	2014	Sweden	White	Prospective	2416	75.4±3.2	100	5 y	8
Güder et al <sup>43</sup>	2009	German	White	Prospective	191	64.4	100	859 d	7
Barrett-Connor et al <sup>44</sup>	1995	United States	White	Prospective	1971	60.4±12.8	52.2	19 y	6
LaCroix et al <sup>45</sup>	1992	Japan	Asian	Prospective	3775	45–68	100	18 y	6
Haring et al <sup>46</sup>	2013	German	White	Prospective	254	75.5	100	10 y	7
Cappola et al <sup>47</sup>	2009	United States	White	Retrospective	950	72.9	49	8 y	7

The subgroup analyses were preplanned for: length of follow-up, 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.<sup>12,13,25–47</sup> 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

**Table 2.** Main Findings of the Eligible Studies

Author	Year	Baseline Diseases	Outcome	Adjustments	HR	Normalized DHEAS	Categories
Blum et al <sup>12</sup>	2013	Acute ischemic stroke	Mortality Poor functional outcome	Age, sex, Charlson index	1.6 (0.85–3.8) 1.23 (1.01–1.49)	91.86 µg/dL (49.76–141.62)	Dichotomous cutoff values Low vs high
Phillips et al <sup>13</sup>	2010	...	ACM CM OM	Age and other covariates/fully adjusted/age and fully adjusted	0.55 (0.43–0.71) 0.4 (0.23–0.7) 0.45 (0.3–0.67)	239.8±99.86 µg/dL	DHEAS logged HR
Maggio et al <sup>25</sup>	2007	...	ACM	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	1.38 (0.84–2.26)	50 µg/dL	Dichotomous cutoff values Low vs high
Cappola et al <sup>26</sup>	2006	Disabled women	Mortality	Age, education, race, smoking status, BMI, estrogen use, corticosteroid use, chronic conditions including CHD, CHF, peripheral artery disease, hip fracture, osteoarthritis, rheumatoid arthritis, DM, cancer, stroke, and COPD	2.05 (1.27–3.32)	≤21.6 µg/dL >21.6, ≤39.7 >39.7, ≤67.9 >67.9	Q1 vs Q3
Page et al <sup>27</sup>	2008	Postmenopausal women	MI	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	1.58 (1.09–2.3)	27.14 µg/dL 27.14–42.49 42.50–64.08 ≥64.09	Q1 vs Q4
Ohlsson et al <sup>28</sup>	2010	...	ACM CM IHD mortality	Age, current smoking, BMI, DM, hypertension, Apolipoprotein B to Apolipoprotein A1 ratio, low testosterone, low estradiol	1.49 (1.17–1.89) 1.61 (1.10–2.38) 1.66 (1.01–2.72)	3.7 µg/dL	Dichotomous cutoff values Low vs high
Shufelt et al <sup>29</sup>	2010	Postmenopausal women with MI	ACM CM	Age, ethnicity, established CVD risk factors	2.26 (1.08–4.75) 2.43 (1.06–5.56)	24.7 µg/dL	Dichotomous cutoff values Low vs high
Hsu et al <sup>30</sup>	2012	CKD hemodialysis men	ACM CM OM	Age, DM, COPD, cardiothoracic ratio, hs-CRP, dialysis duration, albumin creatinine	2.93 (1.09–7.89) 3.81 (0.91–15.9) 2.18 (0.52–9.05)	7.9 µg/dL	Dichotomous cutoff values Low vs high
Trivedi et al <sup>31</sup>	2001	...	ACM CM	Age, BP, BMI, cholesterol, current smokers, steroid use, hormone replacement therapy use, history of CVD or cancer	Men 1.37 (0.91–2.08) 1.79 (1.03–3.13)	61.24 µg/dL 61.24–95.69 95.70–145.45 >145.45	Q1 vs Q4

Continued

Table 2. Continued

Author	Year	Baseline Diseases	Outcome	Adjustments	HR	Normalized DHEAS	Categories
	2001	...	ACM CM	Age, BP, BMI, cholesterol, current smokers, steroid use, hormone replacement therapy use, history of CVD or cancer	Women 0.87 (0.53–1.45) 0.84 (0.41–1.72)	38.28 µg/dL 38.28–57.41 57.42–80.03 >80.04	Q1 vs Q4
Jansson et al <sup>32</sup>	1998	Acute MI	CM	Univariate	1.79 (0.84–3.70)	176.07 µg/dL (145.45–202.87)	Q1 vs Q4
Forti et al <sup>33</sup>	2012	...	ACM	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	1.45 (0.98–2.17)	≤57.42 µg/dL 57.43–86.51 86.52–135.88 ≥135.89	Q1 vs Q4
Jankowska et al <sup>34</sup>	2010	CHF	CM and unplanned hospitalization	Beck Depression Inventory, serum total testosterone, LVFF, BMI, CHF etiology, CAD vs non-CAD, plasma NT-proBNP, eGFR, NYHA class, hemoglobin, age, DM Variables selected based on stepwise approach	1.95 (1.23–3.10)	6.48 µg/dL (3.60–13.15)	Dichotomous cutoff values Low vs high
Jiménez et al <sup>35</sup>	2013	...	Ischemic stroke	Age, ancestry, menopausal status, hormone use, smoking, date of blood collection, BMI, aspirin use, alcohol intake, physical activity, Alternative Healthy Eating Index, history of DM, hypertension, and CHD, or revascularization, glycated hemoglobin, and total/HDL-C	1.44 (0.93–2.23)	<42 µg/dL 42–65.2 65.6–101 >101.5	Q1 vs Q4
Sanders et al <sup>36</sup>	2010	...	CVD	All factors in the full model plus mean age, BMI, and cholesterol. CVD or CHD and CBD were added separately	1.46 (1.03–2.05)	55.5 µg/dL ±41.4	Dichotomous cutoff values
Feldman et al <sup>37</sup>	2001	...	IHD	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	1.97 (1.12–3.48)	2.7–15.9 µg/dL 16.0–23.4 23.5–33.0 33.1–123	Q1 vs Q4
Ponholzer et al <sup>38</sup>	2009	...	CVD	No mention	1.85 (1.05–3.23)	50 µg/dL	Dichotomous cutoff values
Glei et al <sup>39</sup>	2006	...	Mortality	Various indicators of health status in 2000	1.41 (1.31–1.52)	54.5 µg/dL	Dichotomous cutoff values
Fukai et al <sup>40</sup>	2011	...	ACM	Age, nutritional parameters, functional parameters, and prevalent disease	4.42 (1.51–12.9)	43 µg/dL	Dichotomous cutoff values

Continued

Table 2. Continued

Author	Year	Baseline Diseases	Outcome	Adjustments	HR	Normalized DHEAS	Categories
Arnlöv et al <sup>41</sup>	2006	...	CVD	Age, smoking, systolic and diastolic BP, hypertension treatment, total cholesterol–HDL-C ratio, DM, and BMI	1.02 (0.90–1.15)	24.50±19.14 µg/dL	Per 1 SD increase in log DHEAS
Tivesten et al <sup>42</sup>	2014	...	CVD CBD	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	0.87 (0.78–0.98) 0.9 (0.79–1.02)	7.1±4.6 µg/dL	Per SD increase
Güder et al <sup>43</sup>	2009	Heart failure	ACM	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	0.97 (0.91–1.03)	73 (36–131) µg/dL	DHEAS per 10 µg/dL
Barrett-Connor et al <sup>44</sup>	1995	...	ACM CM IHD mortality	Age, BP, smoking, total cholesterol, BMI, fasting plasma glucose, and replacement estrogen	0.93 (0.9–0.95) 0.94 (0.84–1.03) 0.96 (0.85–1.05)	154 µg/dL	A 50-µg/dL decrease in risk ratio
LaCroix et al <sup>45</sup>	1992	...	MI	Systolic BP, serum cholesterol, subscapular skinfold, serum glucose, diabetes mellitus medication, alcohol, physical activity index	0.72 (0.45–1.14)	5–65 µg/dL 66–92 93–114 115–140 141–277	100-µg/dL difference
Haring et al <sup>46</sup>	2013	...	ACM CVD	Age, BMI, smoking, total cholesterol, HDL-C, type 2 DM, systolic BP, and antihypertensive medication	1.18 (0.96–1.45) 1.00 (0.82–1.22)	99.52 (70.81–46.22) µg/dL	Variability (per Q increment)
Cappola et al <sup>47</sup>	2009	...	Mortality	Age, sex, race, CVD, pulmonary disease, DM, cancer, depression	1.89 (1.47–2.43)	0.82 (0.51–1.2) µg/dL	Variability (per SD)

ACM indicates all-cause mortality; BP, blood pressure; CAD, coronary artery disease; CBD, cerebrovascular disease; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CM, cardiovascular mortality; COPD, chronic obstructive pulmonary disease; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hs-CRP, high serum C-reactive protein; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OM, other mortality; Q, quartile.

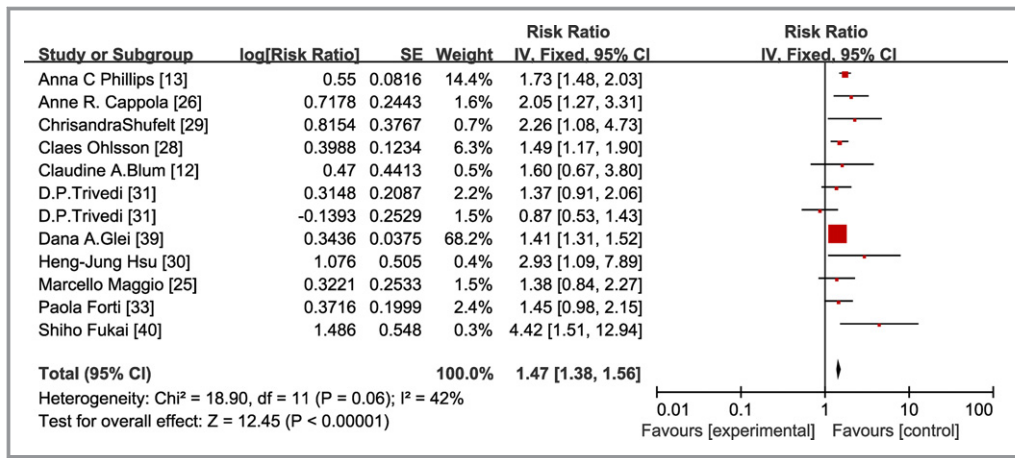


Figure 2. The relationship between dehydroepiandrosterone sulfate and all-cause mortality.

and ranked according to their sum scores (Table 1), of which 21 studies were graded as “good” (scores >6) and 4 as “moderate” (scores ≤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.<sup>41–47</sup> 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

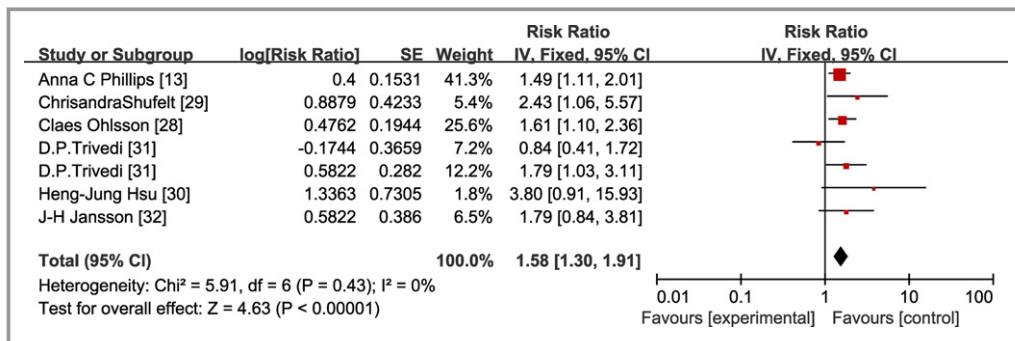


Figure 3. The relationship between dehydroepiandrosterone sulfate and fatal cardiovascular events.

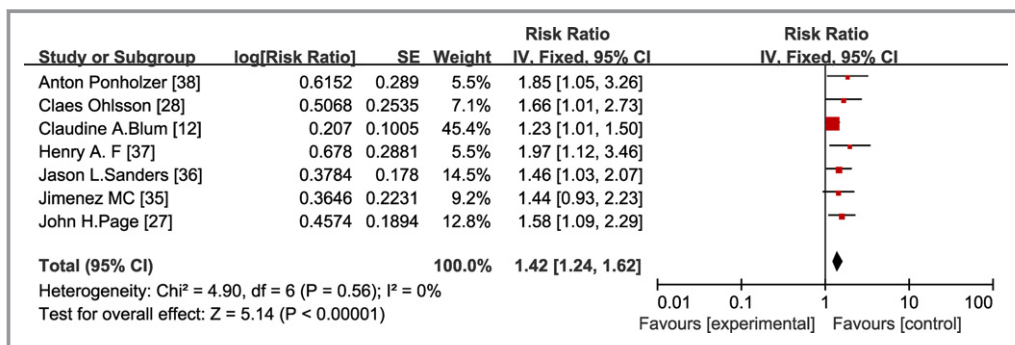


Figure 4. The relationship between dehydroepiandrosterone sulfate and nonfatal cardiovascular events.

**Table 3.** Subgroup Analysis (ACM)

Subgroup	Design	No. of Studies	Sample Sizes	Heterogeneity		Meta-Analysis	
				$I^2$	<i>P</i> 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 categories as quartiles	Yes	4	7848	0	0.03	1.39	1.12–1.73
	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)

Subgroup	Design	No. of Studies	Sample Sizes	Heterogeneity		Meta-Analysis	
				$I^2$	<i>P</i> 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 categories as quartiles	Yes	3	2257	0	0.05	1.45	0.99–2.12
	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)

Subgroup	Design	No. of Studies	Sample Sizes	Heterogeneity		Meta-Analysis	
				$I^2$	<i>P</i> 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 categories as quartiles	Yes	3	66 819	0	0.0003	1.60	1.24–2.06
	No	4	4111	0	0.0001	1.35	1.16–1.58

DHEAS indicates dehydroepiandrosterone sulfate; HR, hazard ratio.



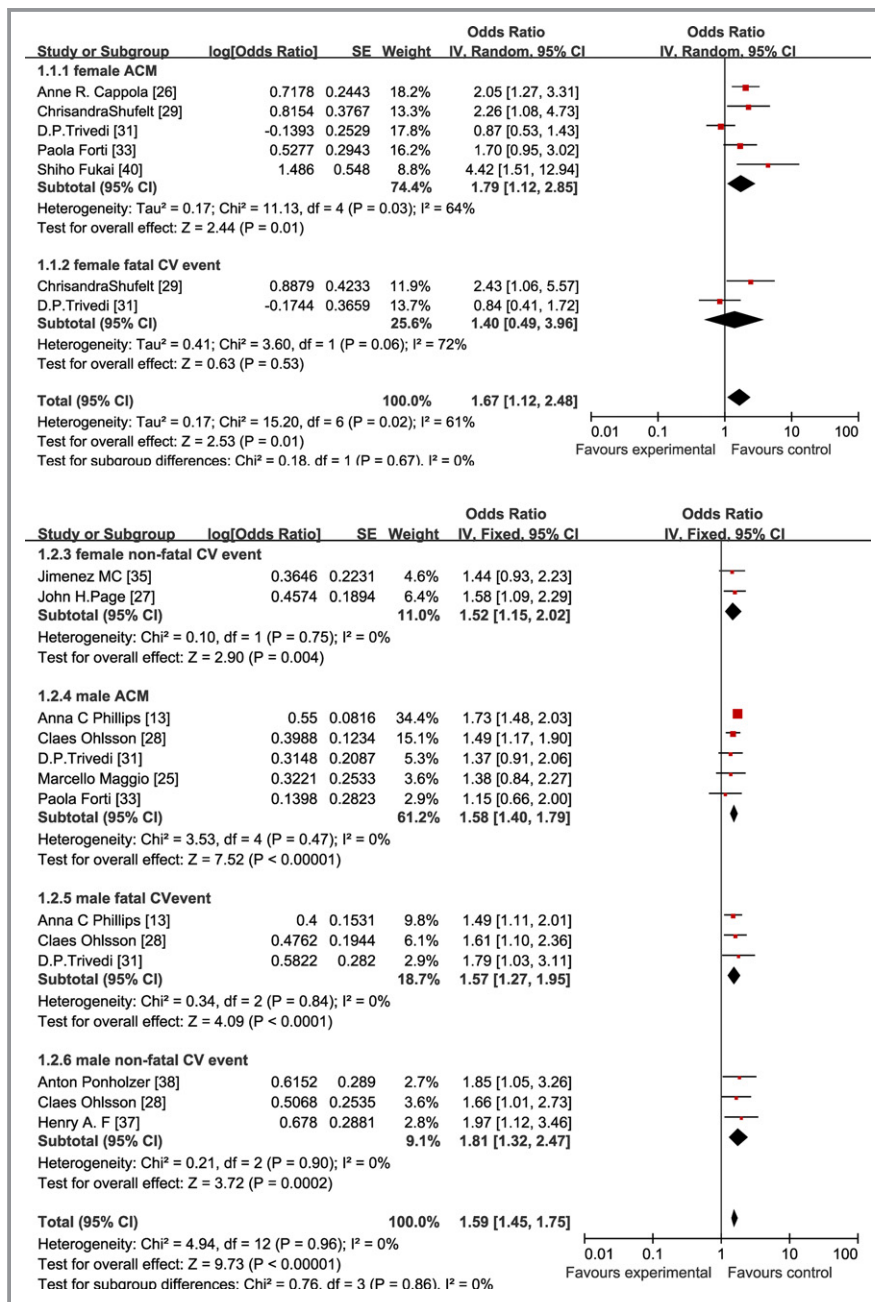
results showed that CVD with low DHEAS was associated with a 47% higher risk of future mortality events (HR, 1.47; 95% CI, 1.38–1.56 [ $P < 0.00001$ ]) (Figure 2).

**DHEAS and fatal/nonfatal cardiovascular events**

Six studies investigated deficient DHEAS level and fatal cardiovascular events,<sup>13,28–32</sup> 7 studies<sup>12,27,28,35–38</sup> investigated low DHEAS and nonfatal cardiovascular events, and 1 study<sup>34</sup> 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 ( $I^2=0%$ ): pooled risk ratio, 1.58 (95% CI, 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% CI, 1.24–1.62;  $P < 0.00001$  [Figure 4]), with no heterogeneity ( $I^2=0%$ ). The HR for the fatal/nonfatal cardiovascular events resulted in a higher association: risk ratio 1.95 (95% CI, 1.23–3.10;  $P = 0.005$ ).



**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.

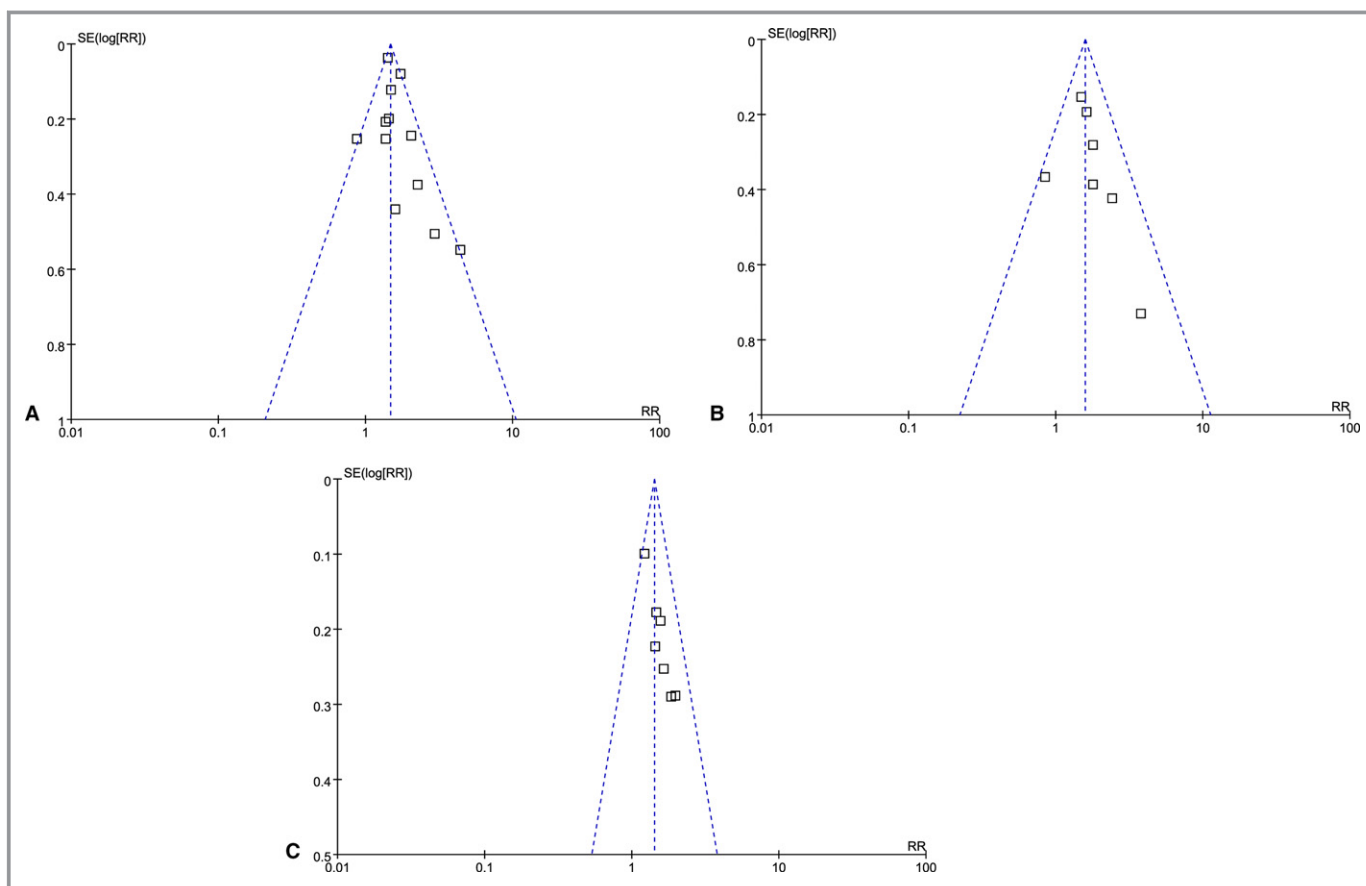
## Discussion

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% CI, 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 morbidity.<sup>20,30,31,36,39,47,48</sup> Similar conclusions in postmenopausal women with low DHEAS levels have been reported and are associated with higher cardiovascular



**Figure 6.** Funnel plots for publication bias test. A, All-cause mortality; (B) fatal cardiovascular events; (C) nonfatal cardiovascular events.

mortality.<sup>27,29</sup> Conversely, no association was observed between DHEAS and mortality in several studies.<sup>49–51</sup> 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.<sup>52</sup>

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.<sup>53–56</sup> Corona et al<sup>57</sup> 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.<sup>58–60</sup> 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.<sup>61,62</sup> A direct role for DHEA in opposing atherosclerosis is suggested by its ability to facilitate fibrinolysis,<sup>63,64</sup> inhibit platelet aggregation, and retard cell proliferation.<sup>65</sup> Previous pathological research elucidated that the zona reticularis, which is responsible for DHEA production, is highly susceptible to vascular damage.<sup>66</sup> 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.

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## Disclosures

None.

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