Are low dehydroepiandrosterone sulphate levels predictive for cardiovascular diseases? A review of prospective and retrospective studies

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Study objective — It has been suggested that low levels of dehydroepiandrosterone sulphate (DHEAS) are predictive for cardiovascular diseases in men. We aimed to review the available evidence from prospective cohort studies and retrospective case-control studies.

Methods — We extracted summary statistics from 4 case-control studies and 8 cohort studies, and calculated the pooled relative risk associated with a 2 µmol/l increase in DHEAS.

Main results — The number of subjects included in each of the individual studies ranged from 94 to 2134, mean age from 48 to 83 years and mean DHEAS levels from 1.2 to 7.3 µmol/l. In men, coronary mortality was available as outcome in 3 cohort studies and 1 case-control study. Combining data from these 4 studies showed a 15% (95% CI: 4%-28%, p = 0.008) increase in fatal coronary heart disease associated with a 2 µmol/l decrease in DHEAS. However, statistical significance was lost when the retrospective study causing significant heterogeneity (p = 0.02) was excluded. Fatal and non-fatal coronary events were reported in 1 cohort study and 3 case-control studies. The average increase in fatal plus non-fatal coronary heart disease associated with a 2 µmol/l decrease in DHEAS amounted to 13% (2%-26%, p = 0.02). The available data did not allow drawing any conclusions on the prognostic value of DHEAS in women, nor on the relationship between DHEAS and total or cardiovascular mortality or stroke in men.

Conclusions — The present findings suggest that, in men, low serum levels of DHEAS may be associated with coronary heart disease. However, whether DHEA supplementation has any cardiovascular benefit is not clear. Data from prospective randomised trials are needed. *(Acta Cardiol 2003; 58(5): 403-410)*

Keywords: *review – dehydroepiandrosterone sulphate (DHEAS) – cardiovascular diseases.*

Introduction

Dehydroepiandrosterone (DHEA) unconjugated or as its sulphate (DHEAS) is the most abundant steroid in the adult human adrenal cortex[1-4]. Both cross-sectional[5-7] and longitudinal[8,9] studies have shown that, in adults, serum levels of DHEA(S) steadily decline with age so that in elderly subjects the serum levels are 20% or less than those observed in young adults[3]. This pattern is observed in both sexes, but DHEA(S) concentrations in women are approximately 50 percent to 70 percent lower than those observed in men[6,10]. The decline of DHEA(S) with age has led to the suggestion that low levels might be associated with diseases of aging[3], such as cardiovascular complications, in particular ischaemic heart disease[11]. Various mechanisms, including effects of DHEA(S) on haemostasis, cell proliferation[12], the metabolism of lipids[13-16] and carbohydrates[15-18], and immune function[19], may explain the apparent relationship with heart disease.

Several epidemiological studies on the relationship between DHEAS and cardiovascular disease have been

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published. Unfortunately, the majority of the available evidence comes from cross-sectional case-control studies in which DHEAS levels were measured after the occurrence of a myocardial infarction[20-22] or the development of coronary arteriosclerosis[7,20,23-25]. Despite differences in study design and case definitions, the majority of these cross-sectional studies found lower levels of DHEAS in male subjects with coronary heart disease as compared to controls[11]. However, these studies do not answer the important question whether the low concentrations of DHEAS in cases compared to controls were the cause rather than the consequence of the cardiovascular disease. The purpose of the present paper was therefore to review the available prospective and retrospective data on the relationship between serum levels of DHEAS and cardiovascular disease.

Methods

Sources of information

Relevant papers and abstracts were identified through a MEDLINE search. Records between January 1980 and December 2002 were searched for the keywords "dehydroepiandrosterone" and "mortality or cardiovascular disease or ischaemic heart disease". In addition, bibliographies of systematic reviews and reference sections of relevant papers were checked. The search was not limited by language. A study was included in the review if it met 2 criteria. First, it had to be a prospective cohort study or a retrospective case-control study on the relationship between DHEAS and outcome. Secondly, it had to report estimates on the predictive value of DHEAS. If the same subjects were included in more than 1 report, only the most recent paper was included in the present review.

Data collection

The analysis was based on published summary statistics. The authors of 6 papers[26-31] were contacted for missing data and for summary statistics that could not be calculated from the published results. However, only 2 of them provided the requested data[27,30]. The definition of events as used by the study investigators was retained for this review. Coronary heart disease was defined as fatal and non-fatal myocardial infarction in 2 studies[32,33], non-fatal myocardial infarction and cardiac death in 1 study[28], and death or hospitalisation due to ischaemic heart disease (IHD, ICD codes 410-414) or intake of medications for IHD or self-reported IHD in another study[27]. Within each study, preference was given to risk ratios adjusted for age, smoking and other relevant risk factors. Whenever possible, men and women were considered separately.

Statistical methods

Database management and statistical analyses were performed using SAS-software version 8.01 (SAS Institute Inc.). The relative risks were combined as described by Hedges et al.[34]. Before applying this method, the relative risk associated with a 2 μmol/l increase in DHEAS was calculated within each study. In the Helsinki Heart Study[28], this relative risk was estimated from the average distance between the tertiles. The relative risks in the individual studies were then transformed to z-scores by taking the antilog. Weighted z-score averages were computed and were used to construct 95 percent confidence intervals for the common effect size[34]. Heterogeneity was assessed using a chi-square statistic. Significant heterogeneity suggests that the results of pooling the data should be interpreted with caution.

Results

Description of individual studies

Of the 13 identified studies[9,27-33,35-39], 1 case-control study[29] was not considered because estimates on the predictive value of DHEAS were not reported and could not be obtained from the authors. Of the remaining 12 studies, 4 had a case-control design and 8 were cohort studies. Their characteristics are summarised in table 1. The number of subjects in each of the individual studies ranged from 94[39] to 2134[31]. Mean age ranged from 48[28] to 83[39] years. In 9 of 12 reports[27,28,30,31,33,36-39], the results were adjusted for age; in 2 studies[9,32] the risk ratios were not adjusted for age and 1 study[35] did not specify whether or not the results were age-adjusted. Several studies also considered additional covariables, such as smoking[28,30-33,37,38], alcohol intake[32], blood pressure[30-33,37,38], cholesterol[31-33,37,38], body size[31,32,37,38], plasma glucose[32,37,38], diabetes or antidiabetic drug intake[32,33,36], oestrogen replacement therapy[31,37], aspirin intake[33], steroid use[31], physical activity[32], level of education[30] and previous health problems[30,31,33,36].

Prognostic significance of DHEAS in men

Ten studies[9,27,28,30-33,35,36,38] reported on the prognostic significance of DHEAS in men (Table 2). However, the end point used varied among studies. Five cohort studies[9,30,31,36,38] and 1 case-control study[35] examined the association between DHEAS and all-cause and/or cardiovascular mortality. Three cohort studies[9,31,38] reported significantly higher risks of total death associated with lower DHEAS levels, while the other 3 studies[30,35,36] observed non-significant relation-

Table 1. – *Characteristics of participants enrolled in reviewed studies*

Name of study	Number	Women (%)	Age* (years)	FU (years)	Mean DHEAS(1) (µmol/l)
Case-control studies					
Helsinki Heart Study[28] (2)	C = 97, E = 62	0	48 (?-?)	4.0	C = 7.0 (3.1), E = 7.7 (4.8)
Honolulu Heart Program[32] (2)	C = 476, E = 238	0	57 (45-68)	18.0	C = 2.7 (1.1), E = 2.6 (1.2)
Physicians' Health Study[33] (2)	C = 169, E = 169	0	? (40-84)	2.3	C = 3.6 (2.2), E = 3.5 (2.3)
Study by Rudman et al.[35] (3)	C = 50, E = 61	0	77 (55-104)	1.0	C = 2.2 (1.3), E = 1.7 (2.3)
Cohort studies					
Cambridge General Practice Health Study[31]	2134	55	70 (65-76)	7.4	2.3 (?)
Helsinki Aging Study[36]	571	74	80 (75-85)	5.0	2.1 (1.4)
Massachusetts Male Aging Study[27]	1167	0	55 (40-70)	8.9	6.8 (3.7)
PAQUID-cohort[9]	595	57	75 (65-?)	7.0	1.7 (1.2)
Rancho Bernardo women[37]	942	100	65.2 (50-88)	19.0	1.9 (?)
Rancho Bernardo men[38]	1029	0	60 (30-82)	19.0	4.5 (?)
Study by Legrain et al.[39]	94	86	83 (65-?)	3.0	1.2 (1.1)
Study by Schaefer et al.[30]	1601	50	? (60-90)	20.0	2.3 (1.6)

C, control group; E, cases; FU, follow-up; *Mean (range), (1) Mean (standard deviation); (2) Cases are patients who experienced a cardiac event; (3) Cases are nursing home men.

Table 2. – *Age-adjusted relative risk associated with dehydroepiandrosterone sulfate in men*

Study	Statistical method*	Adjustment	Mortality			Fatal and nonfatal events		
			Total	CV	CHD	CV	Stroke	CHD
Case-control studies								
Helsinki Heart Study[28]	L (+2 µmol/l)	A,S	…	…	…	…	…	1.23 (0.78-2.00)
Honolulu Heart Program[32]	L (+2 µmol/l)	S,O	…	…	0.55 (0.27-1.05)	…	…	0.77 (0.54-1.11)
Physicians' Health Study[33]	L (+2 µmol/l)	A,S	...	...	...	...	...	0.91 (0.62-1.18)
Study by Rudman et al.[35]	?	?	ns	ns	…	…	…	…
Cohort studies								
Cambridge General Practice Health Study[31]	C (Q2-4 vs Q1)	A,S,O	0.70 (0.50-0.96)	0.57 (0.38-0.86)	…	…	…	…
Helsinki Aging Study[36]	C	A,D	ns	ns	…	…	…	…
Massachusetts Male Aging Study[27]	L (+2 µmol/l)	A	…	…	1.00 (0.77-1.29)	…	…	0.89 (0.79-0.99)
PAQUID-cohort[9]	C (Q2-4 vs Q1)	–	0.5 (0.4-0.8)	…	…	…	…	…
Rancho Bernardo men[38]	C (+2 µmol/l)	A,S,O	0.89 (0.85-0.92)	0.91 (0.76-1.05)	0.94 (0.78-1.08)	…	…	…
Study by Schaefer et al.[30]	C (+2 µmol/l)	A,S,O	0.95 (0.86,1.05)	…	0.84 (0.71-1.02)	…	…	…

CV = cardiovascular; CHD = coronary heart disease.
*L = logistic regression; C = Cox regression; +2 µmol/l = change in DHEAS for which relative risk was determined; Q2-4 vs Q1 = upper 3 quartiles versus first quartile.
A = adjusted for age, S = adjusted for smoking, D = adjusted for diseases (healthy or not healthy), O = adjusted for other relevant risk factors, ns = not significant.

ships. One cohort study[31] found a 75 percent (95 percent confidence interval [95% CI]: 16 percent-163 percent, p = 0.007) higher cardiovascular death rate in men with DHEAS level < 1.60 µmol/l as compared to men with DHEAS above this threshold. However, 3 other studies[35,36,38] reported non-significant relationships between DHEAS and cardiovascular mortality.

Relative risks for fatal coronary heart disease were available in 4 studies[27,30,32,38]. None of the studies found a significant relationship between DHEAS and

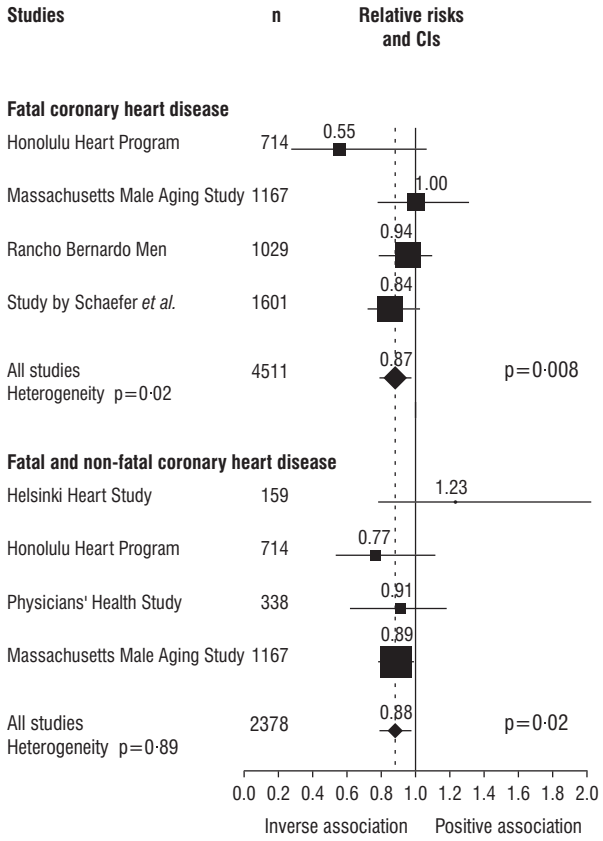

Fig. 1. – Association between DHEAS and fatal (top panel) and fatal plus non-fatal (bottom panel) coronary heart disease. Solid squares and diamonds represent relative risks and 95% confidence intervals associated with a 2 µmol/l increase in DHEAS and have a size proportional to the standard error of the estimate.

fatal coronary heart disease (table 2). Figure 1 (top panel) shows the relative risks associated with a 2 µmol/l increase in DHEAS in each of the 4 studies. The risk of fatal coronary heart disease tended to increase with decreasing DHEAS levels in 3 studies, while in the fourth study the relative risk was 1. There was significant heterogeneity (p = 0.02) across the 4 studies, which was attributable to the tendency towards a 45 percent decrease (95% CI: –5 percent to 83 percent) in the risk of fatal myocardial infarction associated with a 2 µmol/l increase in DHEAS in the Honolulu Heart Program[32]. Combining data from the 4 studies showed a 15 percent (95% CI: 4 percent – 28 percent, p = 0.008) increase in fatal coronary heart disease associated with a 2 µmol/l decrease in DHEAS. However, after exclusion of the retrospective Honolulu Heart Program the relative risk weakened to 0.91 (95% CI: 0.82 – 1.03, p = 0.10).

Fatal and non-fatal cardiovascular events and fatal and non-fatal stroke were not considered as an end point in any of the studies.

One cohort study[27] and 3 case-control studies[28,32,33] reported on the association between DHEAS and fatal plus non-fatal coronary heart disease (table 2). The relative risks associated with a 2 µmol/l increase in DHEAS in each of the 4 studies are illustrated in figure 1 (bottom panel). The risk of coronary heart disease tended to increase with decreasing DHEAS levels in 3 of the 4 studies. However, statistical significance was reached in only 1 study[27]. Heterogeneity was not significant by the chi-square statistic (p = 0.89). When the 4 studies were combined, the risk of coronary events increased by 13 percent (95% CI: 2 percent – 26 percent, p = 0.02) for each 2 µmol/l decrease in DHEAS.

Table 3. – *Age-adjusted relative Risk Associated with dehydroepiandrosterone sulfate in women*

Study	Statistical method*	Adjustment	Mortality			Fatal and nonfatal events		
			Total	CV	CHD	CV	Stroke	CHD
Case-control studies								
Cambridge General Practice Health Study[31]	C(Q2-4 vs Q1)	A,S,O	1.08 (0.71-1.63)	1.15 (0.62-21.1)	…	…	…	…
Helsinki Aging Study[36]	C (?)	A,D	ns	ns	…	…	…	…
PAQUID-cohort[9]	C (Q2-4 vs Q1)	–	1.25 (0.83-2.00)	…	…	…	…	…
Rancho Bernardo cohort[37]	C (+2 µmol/l)	A,S,O	0.91 (0.73-0.95)	1.17 (0.72-1.38)	0.88 (0.78-1.28)	…	…	…
Study by Legrain et al.[39] (86% women)	?	A	ns	…	…	…	…	…
Study by Schaefer et al.[30]	C (+2 µmol/l)	A,S,O	1.14 (1.00-1.31)	…	1.12 (0.89-1.51)	…	…	…

CV = cardiovascular; CHD = coronary heart disease.
*L = logistic regression; C = Cox regression; +2 µmol/l = change in DHEAS for which relative risk was determined; Q2-4 vs Q1 = upper 3 quartiles vs. lower quartile.
A = adjusted for age, S = adjusted for smoking, D = adjusted for diseases (healthy or not healthy), O = adjusted for other relevant risk factors, ns = not significant.

Prognostic significance of DHEAS in women

Six cohort studies[9,30,31,36,37,39] reported on the prognostic significance of DHEAS in women (table 3). Five of the six studies found non-significant relationships between DHEAS and all cause[9,30,31,36,39], cardiovascular[31,36] and coronary heart disease[30] mortality. In the Rancho Bernardo cohort[37], a decrease in DHEAS of 2 μmol/l was associated with a significant 10 percent (95% CI: 5 percent – 37 percent) increase in all-cause mortality. However, in the same cohort, DHEAS was not related to cardiovascular or coronary heart disease mortality. Pooled relative risks were not calculated because in 4 of the 6 studies the relative risks associated with a 2 μmol/l increase in DHEAS were not reported and could not be calculated from the available data.

Discussion

The present review showed that the available data on the prognostic significance of DHEAS are scarce. In addition, characteristics of the patients, definition of end points, confounding factors and statistical methods differed across studies. The pooled results of 4 studies suggested that low DHEAS might be predictive of coronary heart disease in men. The available data did not allow drawing any conclusions on the prognostic value of DHEAS in women, nor on a relationship between DHEAS and total or cardiovascular mortality or stroke in men.

There may be several explanations for the observed inverse association between DHEAS and coronary heart disease in men. First, DHEAS may play a direct role in the pathogenesis or prevention of coronary heart disease. Based on the observation that DHEA has an inhibitory effect on cell growth and proliferation, it has been suggested that decreased DHEAS levels may promote proliferation of vascular intimal cells and the formation of atherosclerotic plaques[40]. Secondly, DHEAS may be indirectly related to coronary heart disease via an effect on lipids, lipoproteins, or other coronary heart disease risk factors. It has been suggested that decreased DHEAS levels may promote the biosynthesis of free fatty acids through inhibition of glucose-6-phophatase dehydrogenase, which is the entry point into the pentose phosphate pathway[12,40,41]. Several studies reported a negative association between DHEAS and total cholesterol[16,42] and a positive association between DHEAS and high-density lipoprotein cholesterol in men, but not consistently in women[13,14,16,24,38,40,43]. The other classical risk factors were not consistently associated with DHEAS in cross-sectional studies. Third, DHEAS may be associated with cardiovascular disease due to confounding with other causal agents such as insulin resistance[44,45], immune responses[19], or neural effects[46]. These factors may be responsible both for the decline in DHEAS and for the onset of coronary heart disease.

In 1987, Barrett-Connor et al.[47] reported, in 289 postmenopausal women from the Rancho Bernardo cohort, a J-shaped relationship between DHEAS and subsequent cardiovascular mortality. Women with DHEAS levels in the highest tertile (> 2.5 μmol/l) had a 12-year cardiovascular mortality rate about twice as high as those in the lowest tertile (< 1.4 μmol/l) and about 5 times as high as in the middle tertile. However, these findings could not be confirmed in a later publication based on a larger cohort and a longer follow-up[37]. The present review showed that the available data are too scarce to draw any conclusions on a possible sex difference in the prognostic value of DHEAS. A sex-specific effect of DHEAS on cardiovascular events can, however, not be excluded. Indeed, Ebeling et al.[1] suggested that DHEA could have both oestrogenic and androgenic effects depending on the hormonal milieu. In men DHEA might bind to vacant oestrogen receptors and enhance oestradiol-like effects, thereby conferring protection against coronary heart disease. By contrast, in postmenopausal women, DHEAS might increase free testosterone concentration, leading to a reduction in HDL-cholesterol and an increased cardiovascular mortality rate[1].

The present analyses assumed a log-linear relationship between DHEAS and outcome. However, some investigators found that only subjects with DHEAS levels in the lowest quartile were significantly more likely to die[9,31] or to experience a coronary event[27] during follow-up. Most published reports did not provide sufficient data to test the hypothesis that only the lowest levels of DHEAS would be associated with an increased risk. As a consequence the relative risks reported in the present paper may have been underestimated.

Comparison of DHEAS levels between populations does not support the hypothesis that low DHEAS levels increase coronary heart disease rates. Indeed, populations, which have the lowest coronary heart disease rates such as the Japanese, also have low mean DHEAS levels[13,32,48]. However, between-population comparisons have major problems of interpretation because of confounding variables. Nevertheless, DHEAS per se does not appear to explain between-population differences in cardiovascular mortality and morbidity.

From the observed inverse association between DHEAS and coronary heart disease, the question of a beneficial effect of DHEA administration arises[3]. We are unaware of any prognostic studies examining the effect of DHEA supplementation on cardiovascular mortality and morbidity. In 1970, 5 of 6 elderly men, aged 65, 66 and 70 years, were relieved from symptoms of advanced angina pectoris within 1 to 4 weeks of initiating 80 mg DHEA per day[49]. Several clinical trials have studied the effects of DHEA administra-

tion on serum lipids[15,50-54]. The oral administration of a very high dose (1600 mg/day during 4 weeks) of DHEA to 5 normal men, aged 22 to 25 years, has been shown to lead to a reduction of 7.1 percent ($p<0.05$) in total cholesterol and 7.5 percent ($p<0.01$) in low-density lipoprotein cholesterol[15]. Similarly, in a randomised 4-week cross-over trial in 6 postmenopausal women[50], a marked decline of 11.3 percent ($p<0.05$) in serum total cholesterol and 20 percent ($p<0.05$) in high-density lipoprotein was observed within one week of DHEA administration (1600 mg/day). In another double-blind randomised placebo-controlled cross-over trial[51], 13 men end 17 women, aged 40 to 70 years, received a replacement dose of 50 mg DHEA per day during 3 months. Serum lipids did not change in men and women, with the exception of high-density lipoproteins in women, which were reduced by 7.7 percent ($p<0.05$). These findings were later confirmed in a similar study[52] using a larger dose (100 mg) of DHEA for a longer duration (6 months) in 8 men and 8 women, aged 50-65 years. As compared to placebo, no changes in serum lipid levels on DHEA were observed, apart from a tendency towards a decrease in high-density lipoproteins by 13.9 percent ($p = 0.07$) in women. Similarly, Casson et al.[53] found that, in a 6-month randomised double-blind placebo-controlled trial in 13 postmenopausal women, DHEA replacement (25 mg/day) resulted in a 19.9 percent ($P<0.05$) decrease in high-density but not low-density lipoprotein. Finally, in a randomised double-blind placebo-controlled trial[54] that examined the effects of 50 mg/day of oral DHEA for 3 months in 60 perimenopausal women, changes in serum lipids were comparable in the intervention and control groups.

Conclusion

In conclusion, the present findings suggest that, in men, reduced serum DHEAS may be associated with coronary heart disease. However, to the best of our knowledge, no long-term trials with cardiovascular disease end points have been reported. Whether administration of DHEA has any cardiovascular benefit is still unestablished.

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References

1. Ebeling P, Koivisto VA. Physiologic importance of dehydroepiandrosterone. *Lancet* 1994; **343**: 1479-81.
2. Hornsby PJ. DHEA: a biologist's perspective. *J Am Geriatr Soc* 1997; **45**: 1395-401.
3. Vermeulen A. Dehydroepiandrosterone sulfate and aging. *Ann N Y Acad Sci* 1995; **774**: 121-7.
4. Hendrikx A. Influence of a low-calorie diet and fasting on the metabolism of dehydroepiandrosterone sulfate in adult obese subjects. *J Clin Endocrinol Metab* 1968; **28**:1525-33.
5. Meldrum DR, Davidson BJ, Tafaryn IV, Judd HL. Changes in circulating steroids with aging in postmenopausal women. *Obstet Gynecol* 1981; **57**: 624-8.
6. Orentreich N, Brind JL, Rizer RL, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab* 1984; **59**: 551-5.
7. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 1991; **73**: 1016-25.
8. Orentreich N, Brind JL, Vogelman J, Andres R, Baldvin H. Long-term longitudinal measurements of plasma dehydroepiandrosteron sulfate in normal men. *J Clin Endocrinol Metab* 1992; **75**: 1002-4.
9. Mazat L, Lafont S, Berr C, Debuire B, Tessier J-F, Dartigues J-F Baulieu EE. Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. *Proc Natl Acad Sci USA* 2001; **98**: 67-9.
10. Kroboth PD, Salek FS, Pittenger AL, Fabian TJ, Frye RF. DHEA and DHEA-S: a review. *J Clin Pharmacol* 1999; **39**: 327-48.
11. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: a review. *Atherosclerosis* 1996; **125**: 1-13.
12. Gordon GB, Bush DE, Weisman HF. Reduction of atherosclerosis by administration of dehydroepiandrosterone. *J Clin Invest* 1988; **82**: 712-20.
13. Okamoto K. Distribution of dehydroepiandrosterone sulfate and relationships between its level and serum lipid levels in a rural Japanese population. *J Epidemiol* 1998; **8**: 285-91.
14. Abbasi A, Duthie EHJ, Sheldahl L, Wilson C, Sasse E, Rudman I, Mattson DE. Association of dehydroepiandrosterone sulfate, body composition, and physical fitness in independent community-dwelling older men and women. *J Am Geriatr Soc* 1998; **46**: 263-73.
15. Nestler JE, Barlascini CO, Clore JN, Blackard WG. Dehydroepiandrosterone reduces serum low density lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. *J Clin Endocrinol Metab* 1988; **66**: 57-61.
16. Shono N, Kumagai S, Higaki Y, Mishizumi M, Sasaki H. The relationships of testosterone, estradiol, dehydroepiandrosterone-sulfate and sex hormone-binding globulin to lipid and glucose metabolism in healthy men. *J Atheroscler Thromb* 1996; **3**: 45-51.
17. Haffner SM, Valdez RA, Mykkänen L, Stern MP, Katz S. Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. *Metabolism* 1994; **43**: 599-603.
18. Paolisso G, Ammendola S, Rotondi M, Gambardella A, Rizzo MR, Mazziotti G, Tagliamonte MR, Carella C, Varricchio M. Insulin resistance and advancing age: what role for dehydroepiandrosterone sulfate? *Metabolism* 1997; **46**: 1281-6.

19. Daynes RA, Araneo BA, Ershler WB. Altered regulation of IL-6 production with normal aging: possible linkage to the age-associated decline in dehydroepiandrosterone and its sulphate derivative. *J Immunol* 1993; **150**: 5219-30.
20. Zumoff B, Troxler RG, O'Connor J, Rosenfeld RS, Kream J, Levin, Sloan AM, Walker W, Cook RL, Fukushima DK. Abnormal hormone levels in men with coronary artery disease. *Atherosclerosis* 1982; **2**: 58-67.
21. Slowinska-Srzednicka J, Zgliczynski S, Ciswicka-Sznajderman M, Srzednicki M, Soszynski P, Biernacka M, Woroszylska M, Ruzyllo W, Sadowski Z. Decreased plasma dehydroepiandrosterone sulfate and dehydrotestosterone concentrations in young men after myocardial infarction. *Atherosclerosis* 1989; **79**: 197-203.
22. Mitchell LE, Sprecher DL, Borecki IB, Rice T, Laskarzewski PM, Rao DC. Evidence for an association between dehydroepiandrosterone sulfate and non-fatal, premature myocardial infarction in males. *Circulation* 1994; **89**: 89-93.
23. Herrington DM, Gordon GB, Achuff SC, Trejo JF, Weisman HF, Kwiterovich PO, Pearson TA. Plasma dehydroepiandrosterone and dehydroepiandrosterone sulfate in patients undergoing diagnositic coronary angiography. *J Am Coll Cardiol* 1990; **16**: 862-70.
24. Adamkiewicz M, Zgliczynski S, Slowinska-Srzednicka J, Pietrzyk E, Rabijewski M, Srzednicki M, Gardas A, Sadowski Z. The relationship between plasma androgens (dehydroepiandrosteron sulfate and testosterone) and coronary arteriosclerosis in men: the lower the androgens, the higher the coronary score of arteriosclerosis. *The Aging Male* 1999; **2**: 22-32.
25. Hauner H, Stangl K, Burger K, Busch U, Blomer H, Pfeiffer EF. Sex hormone concentration in men with angiographically assessed coronary artery disease – relationship to obesity and body fat distribution. *Klin Wochenschr* 1991; **69**: 664.
26. Berr C, Lafont S, Debuire B, Dartigues J-F, Baulieu E-E. 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**: 13410-5.
27. 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.
28. Hautanen A, Mänttäri M, Manninen V, Tenkanen L, Huttunen JK, Frick MH, Adlercreutz H. Adrenal androgens and testosterone as coronary risk factors in the Helsinki Heart Study. *Atherosclerosis* 1994; **105**: 191-200.
29. Contoreggi CS, Blackman MR, Andres R, Muller DC, Lakatta EG, Fleg JL, Harman SM. Plasma levels of estradiol, testosterone, and DHEAS do not predict risk of coronary artery disease in men. *J Androl* 1990; **11**: 460-70.
30. Schaefer C, Friedman G, Ettinger B, Quesenberry C, Liu J, Haan M, Orentreich N, Vogelman J. Dehydroepiandrosterone sulfate (DHEAS), angina, and fatal ischemic heart disease. *Am Epidemiol* 1996; 143, S69. [Abstract].
31. Trivedi DP, Khaw K-T. Dehydroepiandrosterone sulfate and mortality in elderly men and women. *J Clin Endocrinol Metab* 2001; **86**: 4171-7.
32. LaCroix AZ, Yano K, Reed DM. Dehydroepiandrosterone sulfate, incidence of myocardial infarction, and extent of atherosclerosis in men. *Circulation* 1992; **86**: 1529-35.
33. Newcomer LM, Manson JE, Barbieri RL, Hennekens CH, Stampfer MJ. Dehydroepiandrosterone sulfate and the risk of myocardial infarction in US male physicians: a prospective study. *Am J Epidemiol* 1994; **140**: 870-5.
34. Hedges LV, Olkin I. Combining estimates of correlation coefficients. *Statistical methods for meta-analysis*, pp 229-36. San Diego: Academic Press, Inc., 1985.
35. Rudman D, Shetty KR, Mattson DE. Plasma dehydroepiandrosterone sulfate in nursing home men. *J Am Geriatr Soc* 1990; **38**: 421-7.
36. Tilvis RS, Kähönen M, Härkönen M. Dehydroepiandrosterone sulfate, diseases and mortality in a general aged population. *Aging Clin Exp Res* 1999; **11**: 30-4.
37. Barrett-Connor E, Goodman-Gruen D. Dehydroepiandrosterone sulfate does not predict cardiovascular death in postmenopausal women. The Rancho Bernardo Study. *Circulation* 1995; **91**: 1757-60.
38. Barrett-Connor E, Goodman-Gruen D. The epidemiology of DHEAS and cardiovascular disease. *Ann N Y Acad Sci* 1995; **29**: 259-70.
39. Legrain S, Berr C, Frenoy N, Gourlay V, Debuire V, Baulieu E-E. Dehydroepiandrosterone sulfate in a long-term care aged population. *Gerontology* 1995; **41**: 343-51.
40. Nafziger AN, Herrington DM, Bush TL. Dehydroepiandrostereone and dehydroepiandrosterone sulphate: their relation to cardiovascular disease. *Epidemiologic Reviews* 1991; **13**: 267-93.
41. Levy HR. Glucose-6-phosphate dehydrogenase. *Adv Enzymol* 1979; **48**: 97.
42. Lopez SA, Wingo C, Hebert JA. Total serum cholesterol and urinary dehydroepiandrosterone in humans. *Atherosclerosis* 1976; **24**: 471.
43. Haffner SM, Mykkänen L, Valdez RA, Katz MS. Relationship of sex hormones to lipids and lipoproteins in nondiabetic men. *J Clin Endocrinol Metab* 1993; **77**: 1610-5.
44. Nestler JE, Clore JN, Blackard WG. Dehydroepiandrosterone: the "missing link" between hyperinsulinemia and atherosclerosis? *FASEB J* 1992; **6**: 3073-5.
45. Tchernof A, Labric F, Belanger A. Obesity and metabolic complications: contribution of dehydroepiandrosterone and other steroid hormones. *J Endocrinol* 1996; **150**: S155-S164.
46. Demirgoren S, Majewska MD, Spivak CE. Receptor binding and electrophysiological effects of dehydroepiandrosterone sulfate, an antagonist of the GABA receptor. *Neuroscience* 1991; **45**: 127-35.
47. Barrett-Connor E, Khaw K-T. Absence of an inverse relation of dehydroepiandrosterone sulfate with cardiovascular mortality in postmenopausal women. *N Engl J Med* 1987; **317**: 711.
48. Khaw K-T. Dehydroepiandrosterone, dehydroepiandroterone sulphate and cardiovascular disease. *J Endocrinol* 1996; **150**: S149-S153.
49. Fassati P, Fassati M, Sonka J. Dehydroepiandrosterone sulfate – a new approach to some cases of angina pectoris therapy. *Aggressologie* 1970; **11**: 445-8.
50. Mortola J, Yen SSC. The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. *J Clin Endocrinol Metab* 1990; **71**: 696-704.
51. Morales AJ, Nolan JJ, Nelson JC, Yen SSC. Effects of replacement does of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* 1994; **78**:1360-7.
52. Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex

steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol* 1998; **49**: 421-32.
53. Casson PR, Santoro N, Elkind-Hirsch K, Carson SA, Hornsby PJ, Abraham G, Buster J E. Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high density lipoprotein: a six-month trial. *Fertil Steril* 1998; **70**: 107-10.
54. Barnhart KT, Freeman E, Grisso JA, Rader DJ, Sammel J, Kapoor S, Nestler JE. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. *J Clin Endocrinol Metab* 1999; **84**: 3896-902.