

Circulating Androgen Levels and Self-reported Sexual Function in Women

Susan R. Davis, MD, PhD

Sonia L. Davison, MD

Susan Donath, MA

Robin J. Bell, MD, PhD

SEXUAL DYSFUNCTION, PRIMARILY low libido, is common among women, with prevalences of 8% to 50% previously reported.¹⁻³ The prevalence appears to increase with age from the third decade³ as well as after oophorectomy.⁴ Although multiple psychosocial and health factors contribute to low sexual desire and arousal,⁵ it has been proposed that endogenous androgen levels are significant independent determinants of sexual behavior in women.^{6,7} Most studies support a therapeutic benefit of testosterone for women experiencing hypoactive sexual desire disorder, and there is increasing use of testosterone for this purpose.⁸⁻¹⁰ It is widely believed that a low serum free testosterone level is the diagnostic marker for the cluster of symptoms described as characterizing "female androgen insufficiency"⁶ based on therapeutic trials⁸⁻¹¹ and expert opinion.^{6,7,12} However, evidence that a low serum testosterone level distinguishes women with low sexual function from others, and that androgen deficiency syndrome can be defined biochemically, is lacking. Therefore, we have investigated whether low self-reported sexual function, assessed using the validated Profile of Female Sexual Function (PFSF)^{13,14} in women aged 18 to 75 years randomly recruited from the community, is associated with low serum androgen levels.

Context It has been proposed that low sexual desire and sexual dysfunction are associated with low blood testosterone levels in women. However, evidence to support this is lacking.

Objective To determine whether women with low self-reported sexual desire and sexual satisfaction are more likely to have low serum androgen levels than women without self-reported low sexual desire and sexual satisfaction.

Design, Setting, and Participants A community-based, cross-sectional study of 1423 women aged 18 to 75 years, who were randomly recruited via the electoral roll in Victoria, Australia, from April 2002 to August 2003. Women were excluded from the analysis if they took psychiatric medication, had abnormal thyroid function, documented polycystic ovarian syndrome, or were younger than 45 years and using oral contraception.

Main Outcome Measures Domain scores of the Profile of Female Sexual Function (PFSF) and serum levels of total and free testosterone, androstenedione, and dehydroepiandrosterone sulfate.

Results A total of 1021 individuals were included in the final analysis. No clinically significant relationships between having a low score for any PFSF domain and having a low serum total or free testosterone or androstenedione level was demonstrated. A low domain score for sexual responsiveness for women aged 45 years or older was associated with higher odds of having a serum dehydroepiandrosterone sulfate level below the 10th percentile for this age group (odds ratio [OR], 3.90; 95% confidence interval [CI], 1.54-9.81; $P=.004$). For women aged 18 to 44 years, having a low domain score for sexual desire (OR, 3.86; 95% CI, 1.27-11.67; $P=.02$), sexual arousal (OR, 6.39; 95% CI, 2.30-17.73; $P<.001$), and sexual responsiveness (OR, 6.59; 95% CI, 2.37-18.34; $P<.001$) was associated with having a dehydroepiandrosterone sulfate level below the 10th percentile.

Conclusions No single androgen level is predictive of low female sexual function, and the majority of women with low dehydroepiandrosterone sulfate levels did not have low sexual function.

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METHODS

Study Sample

Women were recruited by the random selection method using an electoral roll database for Victoria, Australia. In Australia, where voting is compulsory, every adult is registered on this roll. The city of Melbourne includes 26.25 electoral areas and rural Victoria includes 10.75 electoral areas. Each electoral area was divided into sampling points of approximately equal numbers of 25 000 each. Melbourne had 105 sampling points and

rural Victoria had 43 sampling points. Starting addresses were selected at random from the electoral roll for

Author Affiliations: Women's Health Program, Department of Medicine, Monash Medical School, Alfred Hospital, Victoria, Australia (Drs Davis and Bell and Ms Donath); Jean Hailes Foundation, Victoria, Australia (Drs Davis, Davison, and Bell); Department of Biochemistry, Monash University, Victoria, Australia (Dr Davison); and Murdoch Children's Research Institute and Department of Paediatrics, University of Melbourne, Melbourne, Australia (Ms Donath).

Corresponding Author: Susan R. Davis, MD, PhD, Women's Health Program, Central and Eastern Clinical School, Monash University, Alfred Hospital, Commercial Road, Prahran, Victoria, 3181 Australia (susan.davis@med.monash.edu.au).

each of the sampling points. Interviews were conducted in person on Saturdays and Sundays between 9:00 AM and 4:00 PM. Eight interviews were conducted per sampling point and only 1 eligible person was recruited per household.

Women were contacted by telephone. Women who were between the ages of 18 and 75 years were invited to participate in the study. Women were excluded during telephone screening if they were pregnant or less than 6 weeks postpartum or if they had experienced any of the following in the preceding 3 months: an acute psychiatric illness; acute renal, liver, cardiovascular disease, or any other acute major illness that would impair overall health and well-being; gynecological surgery; active malignancy or cancer treatment, excluding nonmelanotic skin cancer.

We further excluded from this analysis women who had potentially confounding conditions including current use of antidepressants, psychiatric medications, or epilepsy medication, abnormal thyroid function (abnormal thyroid stimulating hormone plus abnormal free thyroxine), polycystic ovarian syndrome, and use of the oral contraceptive pill among women younger than 45 years. Polycystic ovarian syndrome was identified on the basis of combinations of menstrual history, ratio of luteinizing hormone to follicle-stimulating hormone higher than 2, calculated free androgen index higher than 4.5, and sex hormone binding globulin lower than 30 nmol/L.

Women provided fasting morning blood samples on the day they completed and returned their questionnaires. Premenopausal women had blood drawn after cycle day 8 and before menstruation to avoid the early follicular phase testosterone nadir. We did not differentiate between mid-follicular and the luteal phase days because the variation across these parts of the cycle in free and total testosterone is minimal.¹⁵

This study was approved by the Southern Health Human Research and Ethics Committee, Clayton, Australia.

All participants provided written informed consent.

Measurement of Sexual Health by the PFSF

The PFSF is a psychometrically validated instrument developed specifically for the measurement of low sexual desire and related symptoms. It consists of the 7 domains of desire, arousal, orgasm, pleasure, sexual concerns, responsiveness, and self image and has no total score.^{13,14} We selected the PFSF because it was developed based on input from women in the community to ensure its relevancy and accuracy for symptoms, feelings, behaviors, and attitudes. The validation of this questionnaire involved premenopausal and postmenopausal Australian women, with specific attention to the linguistic validity in Australian women.¹³

Biochemical Measurements

Fasting serum samples were stored at -80°C until assayed. Total testosterone was measured by a highly sensitive direct manual radioimmunoassay (Biosource Europe SA, Nivelles, Belgium) in the laboratory of Mayne Health Dorevitch Pathology (Melbourne, Australia) using antibody-coated tubes and 500 μL of iodine-labeled T tracer. For 100 participants, between-batch coefficients of variation were 12.8% at 4.89 ng/dL (0.17 nmol/L), 9.7% at 17.58 ng/dL (0.61 nmol/L), 8.8% at 51.01 ng/dL (1.77 nmol/L), and 7.1% at 331.41 ng/dL (11.5 nmol/L). For 20 participants, within-batch coefficients of variation were 10.5%, 5.3%, 4.2%, and 4.7% at the same concentrations, respectively. Samples with values below 5.76 ng/dL (0.2 nmol/L) (3.1% of all samples) were reported as less than 5.76 ng/dL, but for statistical analysis we assigned these samples a value of 2.88 ng/dL (0.1 nmol/L) because all calculations were performed using Système International units. We reassessed the performance of this assay against a validated and widely published radioimmunoassay following organic solvent (ratio of solution of 3 parts ethylacetate to 2 parts hexane) extraction and celite col-

umn chromatography¹⁶⁻¹⁸ and were satisfied with a high level of consistency between assays. Free testosterone was calculated using the Sodergard equation as previously described.¹⁹ Dehydroepiandrosterone sulfate (DHEAS) and sex hormone binding globulin were measured using a solid-phase, 2-site chemiluminescent enzyme immunometric assay with the Immulite 2000 automated analyzer (Diagnostic Products Corporation, Los Angeles, Calif). The intra-assay and interassay coefficients of variation for sex hormone binding globulin are 6.5% and 8.7%, respectively; the detection limit is 0.2 nmol/L. For DHEAS level, the intra-assay coefficient of variation is between 6.8% and 9.5% and the interassay coefficient of variation is between 9.2% and 12.7%. Androstenedione was measured by direct radioimmunoassay (DSL Inc, Webster, Tex). Follicle-stimulating hormone, thyroid-stimulating hormone, luteinizing hormone, and prolactin were measured using the Vitros ECI machine (Johnson & Johnson, Clinical Diagnostics Division, Rochester, NY).

Sample Size

Other community-based studies suggest a prevalence of self-reported sexual dysfunction among women ranging from 8% to 50%.¹⁻³ Therefore, we powered this study with a conservative estimate that 10% of the study population would report low sexual function and that women with low sexual function would be twice as likely to have a low androgen level (defined as less than the 10th percentile) than other women. Based on these assumptions our estimated required sample size was 1100 ($\alpha = .05$; $1 - \beta = .80$). The distribution of the domain of sexual concerns differed from the other domains with more than 20% of women in each age group reporting the maximum score. Therefore, we excluded the domain of sexual concerns from our analysis.

The proportion of women reporting a zero score (from a possible range of 0-100) for sexual satisfaction varied for the domains of the PFSF from

2.7% for responsiveness to 12.8% for sexual arousal.

Statistical Analysis

The number of women who answered the questions varied slightly. The PFSF domain scores were not normally distributed. Because the pattern of self-reported sexual satisfaction differed according to age, data analyses were stratified by age (<45 years vs ≥45 years). The decline in testosterone is greatest between the third and fifth decades,²⁰ does not change during menopause,²¹ and changes very little with age in postmenopausal women,²² providing additional support for this approach.

For all the PFSF domains among older women, the proportion of women reporting a score of zero (of a possible 100) determined the “low” sexual satisfaction score (between 4% and 17% for each domain). For younger women, less than 4.8% reported zero for 2 of the PFSF domains. Hence, to provide consistency and avoid overdiagnosing low sexual function, we set a level of 5% for the category of low in the other 4 domains for younger women.

Receiver Operating Characteristic Curves

We looked at the relationships between the dichotomous variable (low vs not low sexual function) and the series of continuous variables, which were the androgen levels. Receiver operating characteristic (ROC) curves were used to compare the relationship between sensitivity and specificity for different cutoff levels for each of the androgens. Whether each androgen was useful for discriminating between individuals with and without low sexual function for each PFSF domain was established by testing whether the area under each ROC curve was significantly different from 0.50.²³

For each of the androgens, where the area under the ROC curve was highly statistically significantly different from 0.50 ($P \leq .01$), the table of coordinate points for the ROC curve was used to identify a cutoff point that would best differentiate those women with low

sexual function from those without low sexual function. The cutoff points were used to generate contingency tables and to calculate odds ratios.

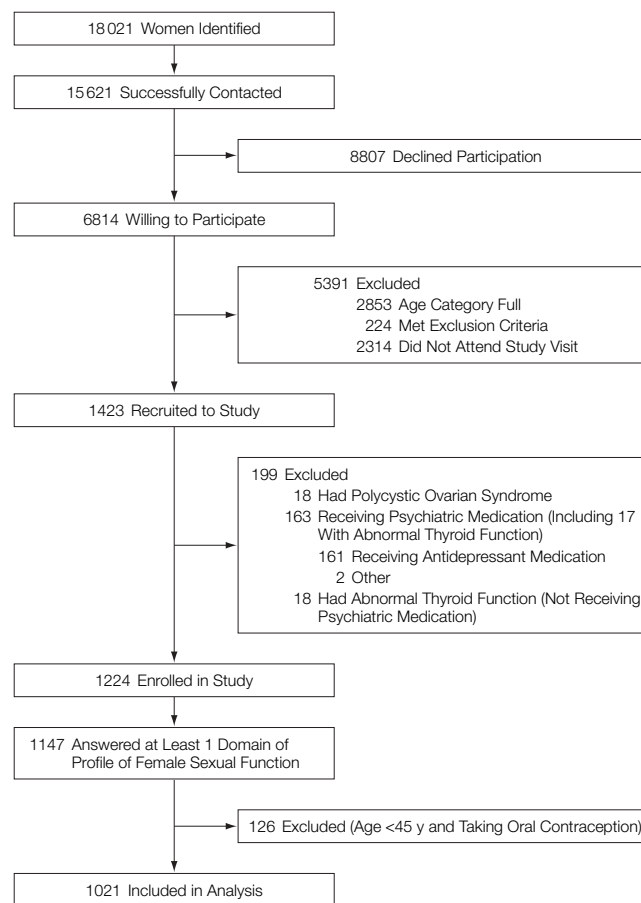
RESULTS

Of a total of 18 021 women, 15 621 were successfully contacted. Of these, 8807 women declined to participate. Of those who wished to participate, 2853 were excluded because their age category was already full and 224 were excluded based on the exclusion criteria. However, only 1423 of the 3737 who had stated they wished to participate attended their study visit. Of the 1423 women recruited to the study, 199 were excluded (FIGURE). Of the remaining 1224 women, 1147 answered at least 1 PFSF domain. Of these, 126 younger women were excluded on the basis of

oral contraceptive use, leaving a total of 1021 in the analysis. The characteristics of the study population appear in TABLE 1.

The ROC curves provided no evidence for total or free testosterone being useful for discriminating between individuals with or without low sexual function for a PFSF domain for younger or older women (TABLE 2 and TABLE 3). In contrast, the areas under the ROC curves for DHEAS levels were highly significantly different from 0.50 ($P \leq .01$) for older women in relation to the domains of arousal, responsiveness, and pleasure, and for younger women, for desire, arousal, and responsiveness. For older women, the area under the ROC curve for androstenedione and pleasure was also highly significantly different from 0.50.

Figure. Recruitment of Study Participants



For some of these highly significant associations in older women for domains where 16.5% or 17.7% of women reported a zero score (DHEAS levels and the domains of arousal and pleasure; androstenedione and pleasure), although a serum androgen level cutoff was identified from the coordinate table of the ROC curve, the cutoff resulted in at least 30% of women being classified as having a low DHEAS level or androstenedione level.

In contrast, for the domain of sexual responsiveness in older women, the reporting of a zero score by 4.1% was associated with a DHEAS level of less than 294.8 ng/mL (0.8 μ mol/L), which was below the 10th percentile for this age

group. The odds ratio for having a DHEAS level below 294.8 ng/mL (0.8 μ mol/L) in older women with low sexual responsiveness compared with those without was 3.90 (95% confidence interval [CI], 1.54-9.81; TABLE 4).

For younger women, the best cutoff suggested by the ROC curve for each of the domains desire, arousal, and responsiveness was a DHEAS level below 773.8 ng/mL (2.1 μ mol/L), which corresponded to the 10th percentile for this age group. The odds ratio for having a DHEAS level below 773.8 ng/mL (2.1 μ mol/L) in younger women and being below the fifth percentile for the PFSF domains of desire were 3.86 (95% CI, 1.27-11.67); arousal, 6.39 (95% CI, 2.30-17.73); and responsiveness, 6.59 (95% CI, 2.37-18.34) compared with women who were above the fifth percentile for these domains (Table 4).

COMMENT

Multiple factors influence sexual behavior. The aim of this study was to explore whether women with low self-reported sexual well-being are more likely to have low serum androgen levels than women without self-reported low sexual well-being.

The PFSF, although validated, had not previously been applied to a large population of women so we were unable to anticipate the pattern of response. The pattern of response determined the definition of low sexual function for older women, that is, the reporting of a zero score, and pro-

vided a justifiable cutoff of 5% for the category of low sexual function in younger women.

We found no evidence of associations between low scores for any of the sexual domains evaluated and low serum total and free testosterone levels. In contrast, we observed significant associations between low sexual desire, arousal, and responsiveness in younger women and low responsiveness in older women and low serum DHEAS level relative to age.

In light of the complexity of sexual function, it is not surprising that the areas under the ROC curves that achieved statistical significance for DHEAS level were not greatly different from 0.50. Exploration of cutoffs identified from the ROC curves suggested that the likelihood of finding a clinically useful association between women identified as having a low sexual function and a low androgen level was greatest when the proportion of women with low sexual function was small (<fifth percentile) and the normal range for the serum androgen level was relatively large, such as the DHEAS level among young women.²²

The main strengths of this study are that we used a validated instrument that demonstrates good discrimination between different levels of self-reported sexual function in younger and older women¹³ to evaluate sexual function, a sensitive radioimmunoassay for the measurement of testosterone, and a community-based population of women from across our state. A potential weak-

Table 1. Characteristics of Study Population*

	No. (%) of Women	
	Recruited to Study (n = 1423)	Provided PFSF Response and Included in Study (n = 1021)
Age, y		
18-24	73 (5.1)	34 (3.3)
25-34	196 (13.8)	111 (10.9)
35-44	282 (19.8)	198 (19.4)
45-54	322 (22.6)	276 (27.0)
55-64	280 (19.7)	209 (20.5)
65-75	270 (19.0)	193 (18.9)
Weight, mean (SD), kg	73.4 (17.0)	73.3 (17.3)
BMI, mean (SD)†	27.8 (6.5)	27.8 (6.6)
Non smoker	1204 (84.6)	877 (85.9)
Current smoker	219 (15.4)	144 (14.1)

Abbreviations: BMI: body mass index; PFSF, Profile of Female Sexual Function.

*Values are expressed as number (percentage) unless otherwise indicated.

†Calculated as weight in kilograms divided by the square of height in meters.

Table 2. Profile of Female Sexual Function Domain Scores for Women Aged 45 to 75 Years*

	Desire	Arousal	Responsiveness	Pleasure	Orgasm	Self-image
No./Total (%) of participants with 0 domain score	55/637 (8.6)	113/638 (17.7)	24/589 (4.1)	103/623 (16.5)	78/609 (12.8)	26/646 (4.0)
DHEAS AUROC	0.51	0.62	0.66	0.58	0.57	0.47
P value	.90	.001	.007	.008	.04	.65
Androstenedione AUROC	0.57	0.56	0.57	0.59	0.55	0.41
P value	.10	.06	.24	.004	.13	.12
Testosterone AUROC						
Total	0.54	0.56	0.57	0.52	0.54	0.41
P value	.38	.06	.23	.60	.22	.12
Free	0.54	0.56	0.59	0.50	0.56	0.43
P value	.34	.04	.13	.96	.08	.21

Abbreviations: AUROC, area under the receiver operating characteristic curve; DHEAS, dehydroepiandrosterone sulfate.

*P values indicate whether the AUROC is different from 0.50 for each Profile of Female Sexual Function domain.

Table 3. Profile of Female Sexual Function Domain Scores for Women Aged 18 to 44 Years*

	Desire†	Arousal‡	Responsiveness§	Pleasure	Orgasm	Self-Image¶
No./Total (%) of participants with low domain score	17/335 (5.1)	18/338 (5.3)	18/336 (5.4)	16/336 (4.8)	16/334 (4.8)	14/339 (4.1)
DHEAS AUROC	0.68	0.68	0.72	0.54	0.56	0.62
<i>P</i> value	.01	.01	.002	.61	.42	.13
Androstenedione AUROC	0.58	0.61	0.66	0.58	0.56	0.60
<i>P</i> value	.25	.12	.02	.28	.41	.19
Testosterone AUROC						
Total	0.58	0.56	0.64	0.54	0.55	0.60
<i>P</i> value	.30	.36	.05	.58	.47	.23
Free	0.59	0.56	0.61	0.50	0.53	0.44
<i>P</i> value	.22	.37	.12	.99	.70	.48

Abbreviations: AUROC, area under the receiver operating characteristic curve; DHEAS, dehydroepiandrosterone sulfate.

**P* values indicate whether the AUROC is different from 0.50 for each Profile of Female Sexual Function domain. The cutoff for the lowest score is 5%.

†Lowest 5 of 46 possible scores.

‡Lowest 2 of 16 possible scores.

§Lowest 7 of 36 possible scores.

||Score of 0.

¶Lowest 3 of 21 possible scores.

ness is that despite our study population being recruited by a random process based on the electoral roll, only 9.1% of those contacted actually participated, indicating that selection pressures were operating, as in any voluntary research project. Specific barriers to participation were the requirements to provide a fasting blood sample, which for participants from regional Victoria, constituting one third of our study population, involved travel to a collection center, and for young women, timing of collection according to their menstrual cycle. The approach we took was to minimize bias. The alternative approach would have been to recruit a convenience sample, which may have achieved a higher participation rate. However in doing so, we would have risked recruiting a biased sample.

A concern might also be that a single serum testosterone level does not reflect serum testosterone over time. Apart from the diurnal variation in testosterone, there is no reason why serum testosterone should vary significantly over days to weeks in postmenopausal women. For premenopausal women, small variations across the mid-follicular and luteal phases would not have affected classification with respect to the lowest 10th percentile. Furthermore, in practice, clinical assessment will usually be made on a single serum sample. Therefore, we believe a single early morning serum sample pro-

Table 4. Relationship Between Low Dehydroepiandrosterone Sulfate Level and Profile of Female Sexual Function Domain Scores*

	No. (%) of Women		OR (95% CI)	<i>P</i> Value
	DHEAS <294.8 ng/mL (0.8 μmol/L)	DHEAS ≥294.8 ng/mL (0.8 μmol/L)		
Responsiveness				
0 (4.1%)	7 (29.2)	17 (70.8)	3.90 (1.54-9.81)	.004
>0	54 (9.6)	511 (90.4)		
Desire†				
Lowest 5.1%	5 (29.4)	12 (70.6)	3.86 (1.27-11.67)	.02
Not low	31 (9.7)	287 (90.3)		
Arousal‡				
Lowest 5.3%	7 (38.9)	11 (61.1)	6.39 (2.30-17.73)	<.001
Not low	29 (9.1)	291 (90.9)		
Responsiveness†				
Lowest 5.4%	7 (38.3)	11 (61.2)	6.59 (2.37-18.34)	<.001
Not low	28 (8.8)	290 (91.2)		

Abbreviations: CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; OR, odds ratio.

*The DHEAS cutoff of 294.8 ng/mL applies to women ≥45 years; the cutoff of 773.8 ng/mL applies to women 18 to 44 years.

†For women aged 18 to 44 years, low desire, arousal, and responsiveness were indicated by being in the cutoff closest to the fifth percentile.

vided a practical classification of women for the purpose of this study.

The hormone we identified as being associated with low self-reported sexual function is DHEAS and not free testosterone. This is most likely due to differing circulating levels of these steroids and the complexity of androgen metabolism. DHEA is the most abundant sex steroid in women²⁴ and circulating DHEA and its sulfate, DHEAS, provide a large precursor reservoir for the intracellular production of both estrogens and androgens.²⁵⁻²⁷ Traditionally, circulating hor-

mon levels have been used as the main indicators of tissue exposure. However, intracrinology plays a pivotal role in androgen metabolism, such that the active androgens exert their effects in the same cells in which they are synthesized, without release into the pericellular compartment.²⁸ DHEA and DHEAS are converted in extragonadal target tissues, such as the brain, bone, and adipose, either to androstenedione or testosterone that may then be aromatized to estrone or estradiol or converted by 5α-reductase to dihydrotestosterone in

the same cells.^{25,29} Thus androgenic effects vary according to individual variations in the amount and activity of the enzymes 5 α -reductase and aromatase, and individual differences in the androgen-receptor response. With substantial androgen production and metabolism being intracrine, measurement of serum testosterone does not provide a specific measure of androgen tissue exposure or action.

In addition to demonstrating that the measurement of testosterone is not useful for the diagnosis of the proposed female androgen insufficiency syndrome,⁶ our findings also do not support a diagnostically useful role for the measurement of DHEAS. This is because despite the increased likelihood that women with low sexual function have a low DHEAS level, the majority of women with a low DHEAS level did not report low sexual function.

Our results are not in conflict with testosterone being used pharmacologically to treat hypoactive sexual desire disorder,^{9,10} nor do they provide support for efficacy of DHEA therapy. Rather, our data, taken together with what is already known about the intracrine physiology, suggest that sex steroids influence female sexual function, but that there is no serum androgen level that defines female androgen insufficiency. The measurement of serum testosterone, free testosterone, or DHEAS in individuals presenting with low sexual function is not informative and levels of these hormones should not be used for the purpose of diagnosing androgen insufficiency in women.

Author Contributions: Dr Bell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Davis, Davison, Donath, Bell.
Acquisition of data: Davis, Davison.
Analysis and interpretation of data: Davis, Davison, Donath, Bell.
Drafting of the manuscript: Davis, Donath, Bell.
Critical revision of the manuscript for important intellectual content: Davis, Davison, Donath, Bell.
Statistical analysis: Donath, Bell.
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Study supervision: Davis.
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