Supplementary Online Content

Basaria S, Harman SM, Travison TG, et al. The effects of testosterone administration for three years on subclinical atherosclerosis progression in older men with low or low normal testosterone levels: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2015.8881

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplementary Table 1. Comparison of baseline characteristics by trial completion status, mean (standard deviation) or N (%) shown.

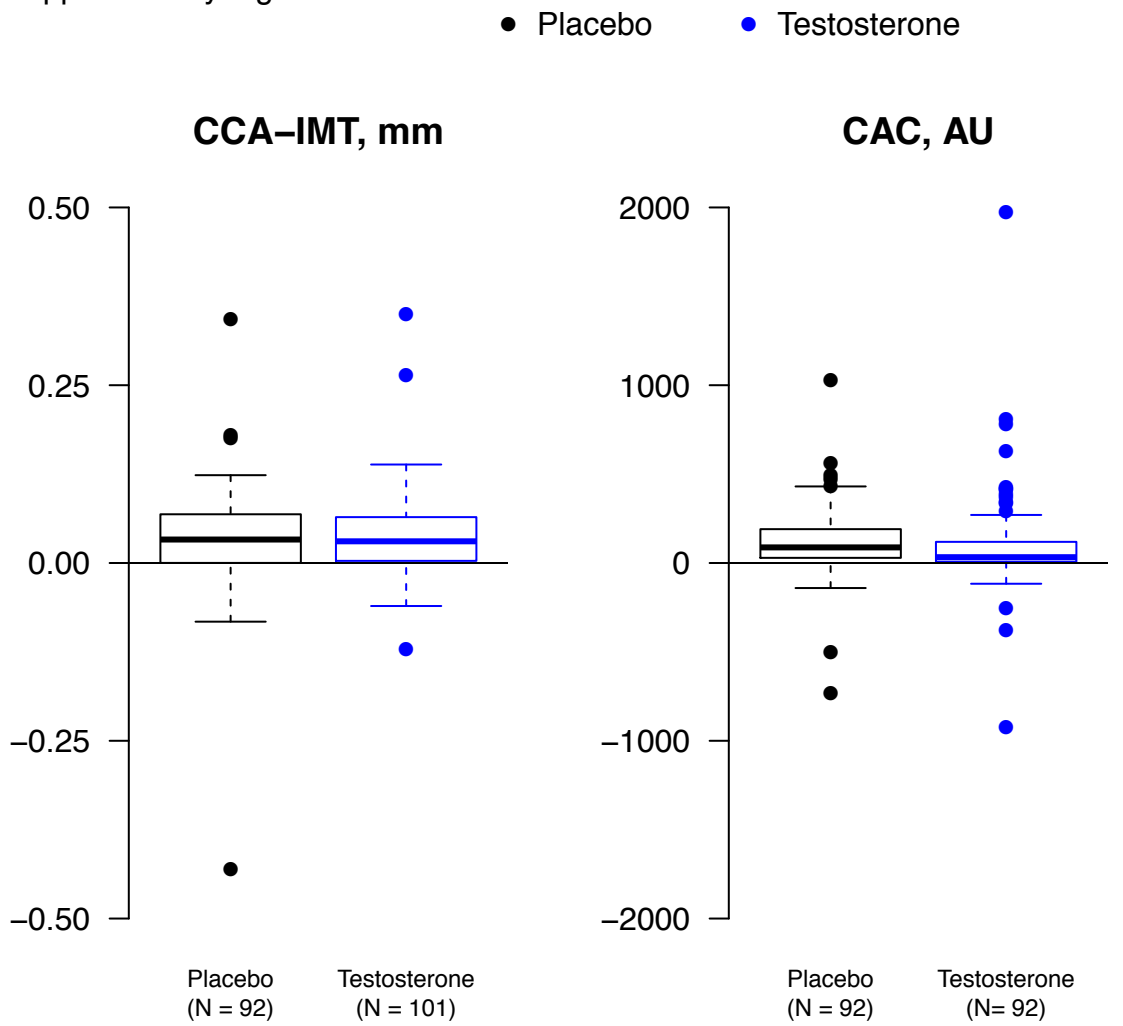
	Completed Trial (N = 211)	Did not complete trial (N = 95)
Age, years	67.2 (5.0)	68.3 (5.4)
BMI, kg/m^2	28.1 (2.8)	28.0 (3.0)
Testosterone, ng/dl	306 (66)	310 (64)
CCA-IMT, mm	0.88 (0.19)	0.88 (0.23)
CAC, AU	443 (681)	565 (754)

Supplementary Table 2. Adverse events associated with randomization to testosterone or placebo arms

	Testosterone (N = 155)		Placebo (N = 151)		
	Number of Events	Participants reporting one or more events	Number of Events	Participants reporting one or more events	[a]p
Cardiovascular	28	20	24	16	0.65
Dermatologic	15	14	13	12	0.76
Endocrine/Metabolic	8	7	6	6	0.63
Gastrointestinal	14	11	17	12	0.54
Genital/Urinary	41	32	31	27	0.29
Hematologic	17	15	4	4	0.011
Hepatic/Biliary	1	1	1	1	0.99
Infectious Disease	-	-	3	3	>0.99
Lymphatic	-	-	2	2	>0.99
Musculoskeletal	37	30	36	27	>0.99
Neurologic	4	4	5	4	0.71
Other	18	16	21	18	0.57
Psychiatric	4	4	5	5	0.71
Pulmonary	21	20	33	27	0.09
SAE	33	25	33	24	0.92

[a]Wald test derived from Poisson regression of count of events per subject on treatment intervention. Thirteen participants in the testosterone arm experienced a hematocrit >54% compared to no participant in the placebo arm. More men in the testosterone (n=14) than placebo (n=2) arm had an IPSS score >21. Major Adverse Cardiovascular Events (MACE) in the testosterone and placebo groups, respectively, were as follows: myocardial infarction: 3 vs 2; coronary revascularization procedure: 5 vs 2; stroke: 3 vs 0; cardiovascular-related death: 1 vs 0.

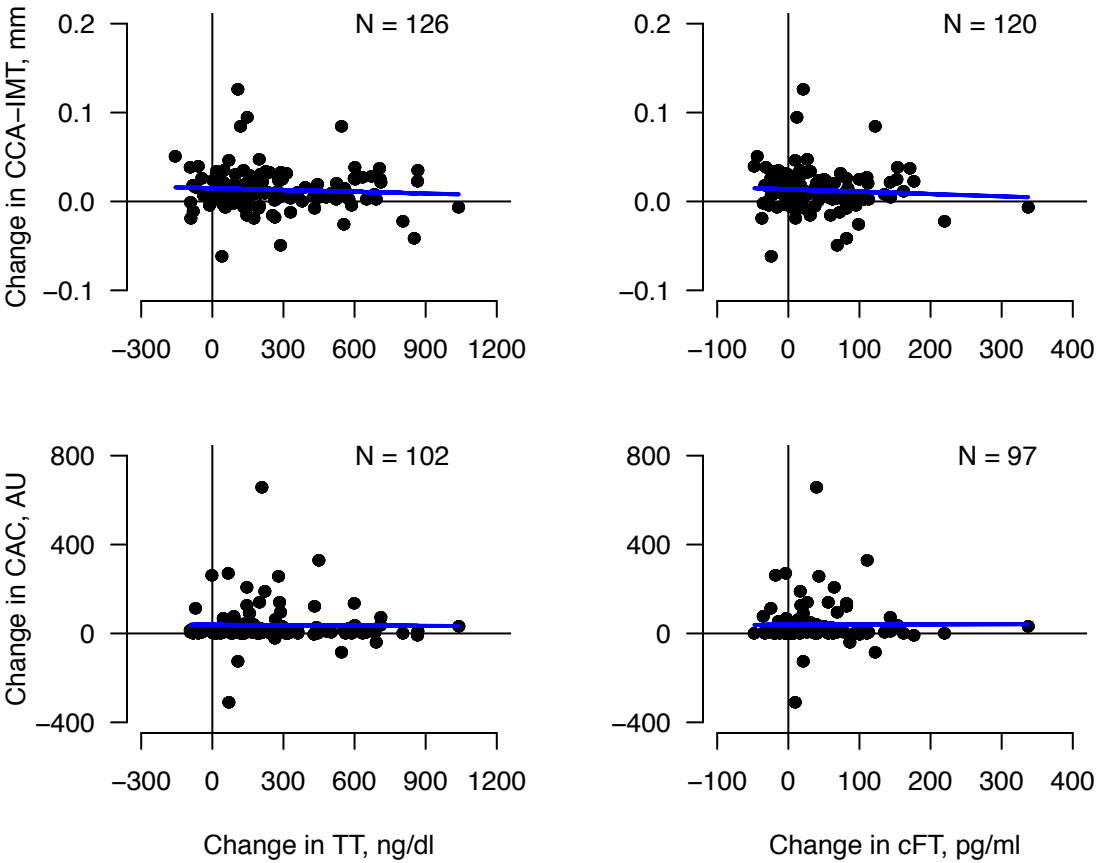
Supplementary Figure 1



Participant level three–year change in carotid artery intima–media thickness (CCA–IMT) and coronary artery calcification (CAC), by randomization group, among participants in the completer sample.

Boxplots show medians (dark horizontal lines), 25th and 75th percentiles (top and bottom, respectively, of solid boxes), upper and lower hinges (dashed lines, extending from 25th and 75th percentiles to the outermost data points within 1.5 interquartile intervals of those percentiles), and values lying outside these ranges (single data points).

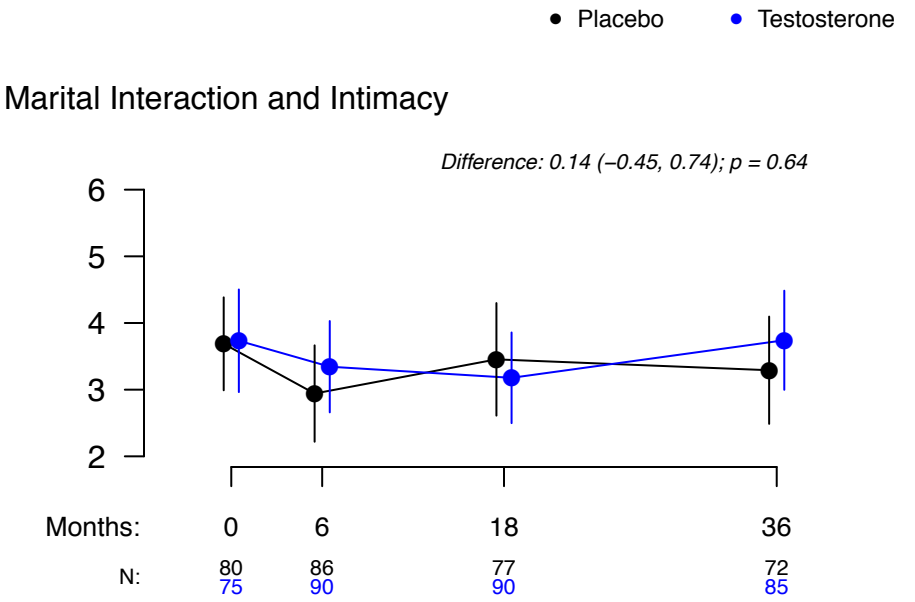
Supplementary Figure 2



Association between change in circulating total testosterone (TT) & calculated free testosterone (cFT) levels and change in common carotid artery intima–media thickness (CCA–IMT) & coronary artery calcification (CAC), using data observed on participants assigned to testosterone replacement.

Participants' changes in CCA–IMT and CAC are summarized as linear trends with time, scaled to one year. Change in total and free testosterone is taken as the difference between mean on–treatment and baseline values. Fitted smooths (blue lines) are obtained via a generalized additive model. Deviance explained for each of these models was less than 0.5%, indicated marked lack of evidence of association.

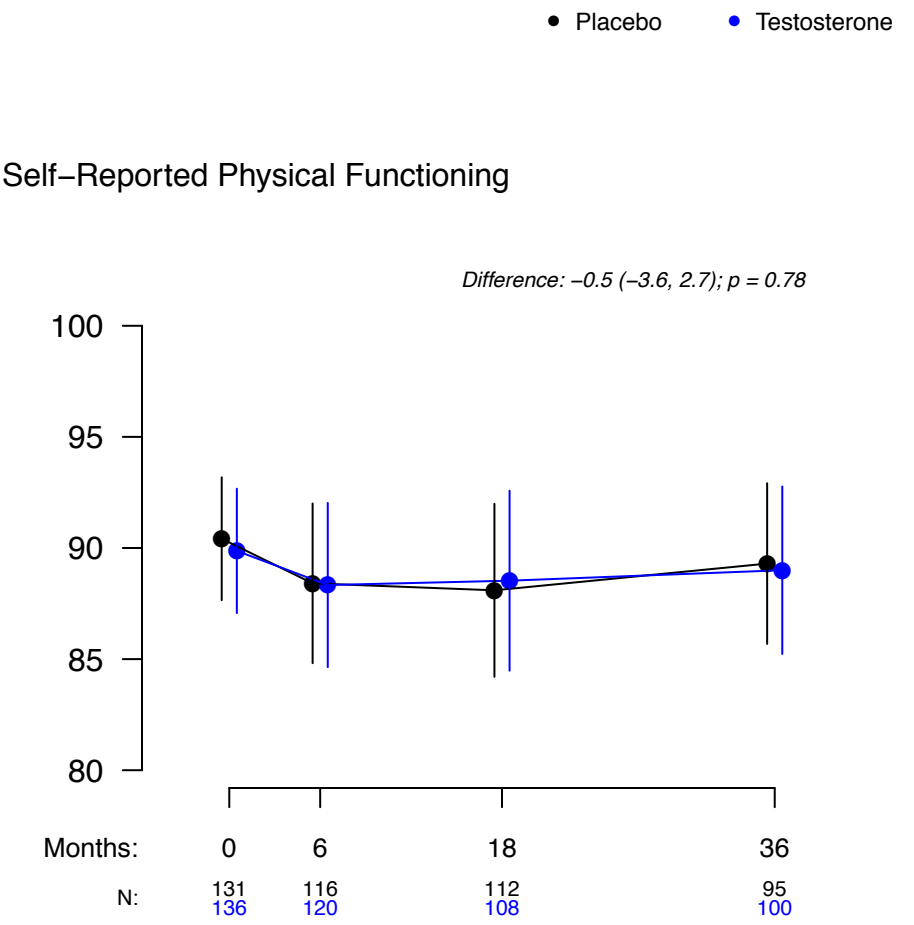
Supplementary Figure 3



Baseline and on−treament data obtained using the Cancer Rehabilitation Evaluation System Short Form (CARES−SF) Marital Subscale.

Sample means and 95% confidence intervals shown for each visit and arm are based on observed data. The model−based estimate of on−treatment difference between arms, controlling for age group and study center, and accommodating missing records via multiple imputation, is provided in italicized text. The number of observed data points at each visit is provided along the horizontal axis.

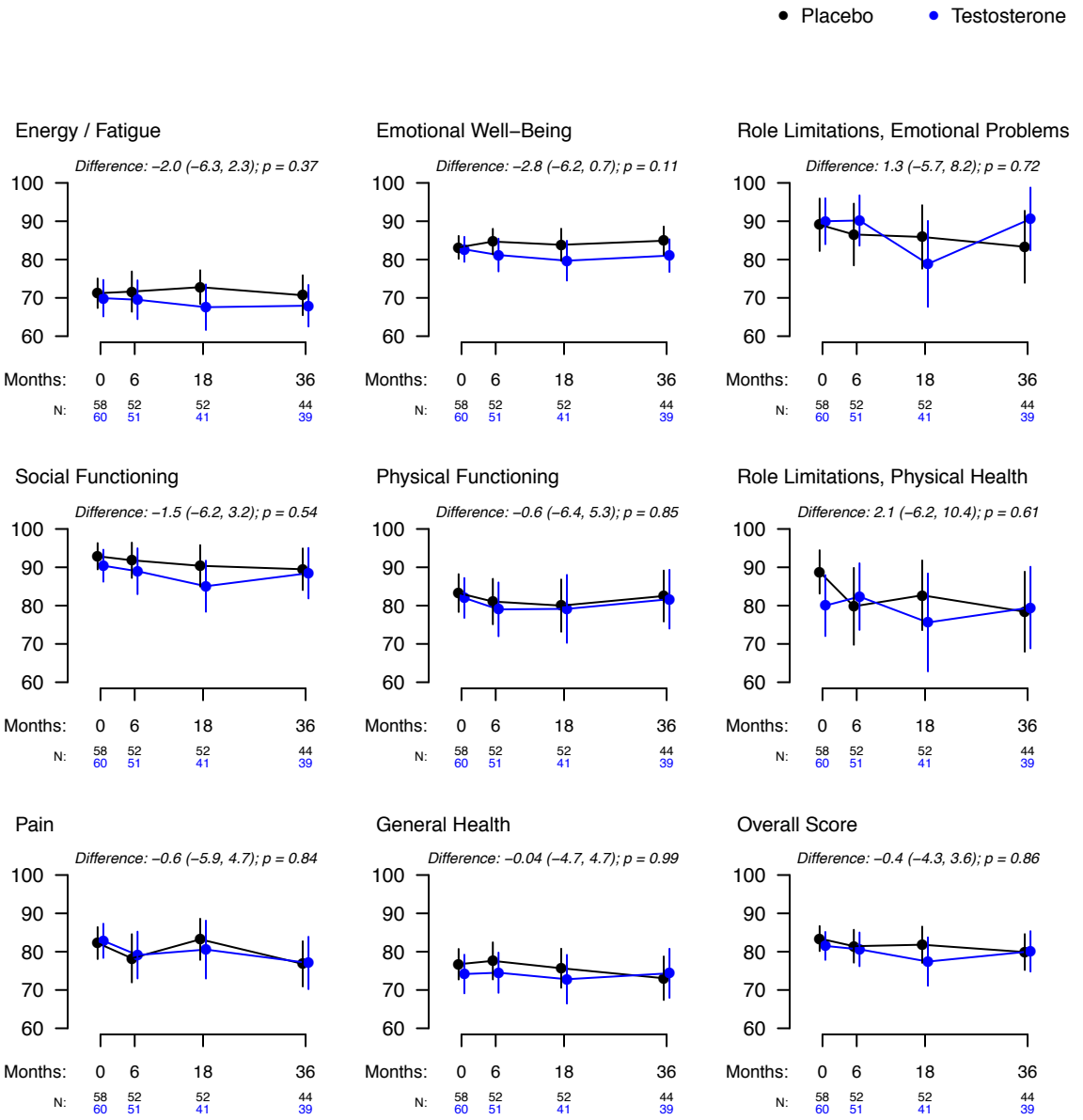
Supplementary Figure 4



Baseline and on−treament data obtained using the physical functioning scale of the MOS 36−item short−form health survey (SF−36).

Sample means and 95% confidence intervals shown for each visit and arm are based on observed data. The model−based estimate of on−treatment difference between arms, controlling for age group and study center, and accommodating missing records via multiple imputation, is provided in italicized text. The number of observed data points at each visit is provided along the horizontal axis.

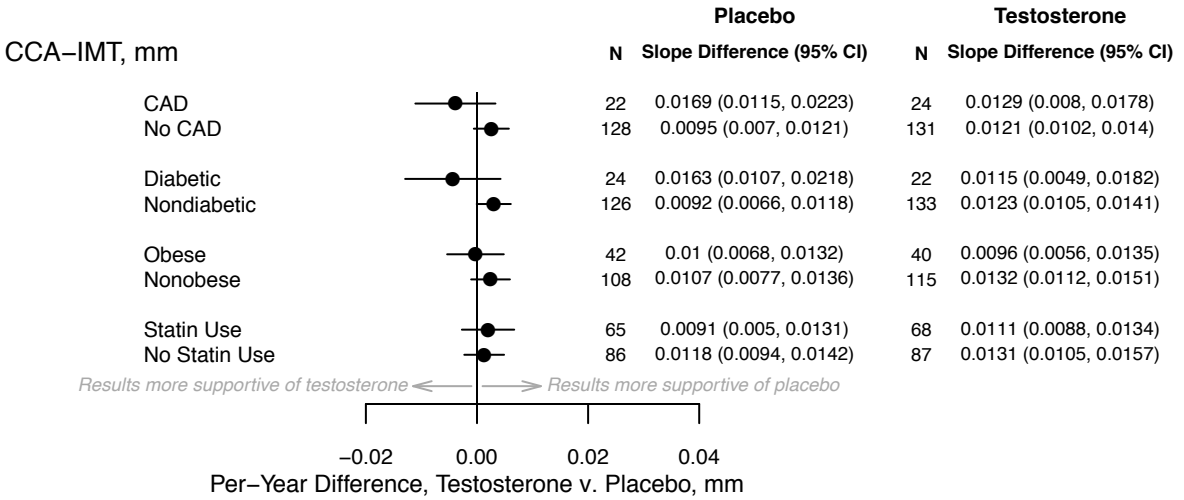
Supplementary Figure 5

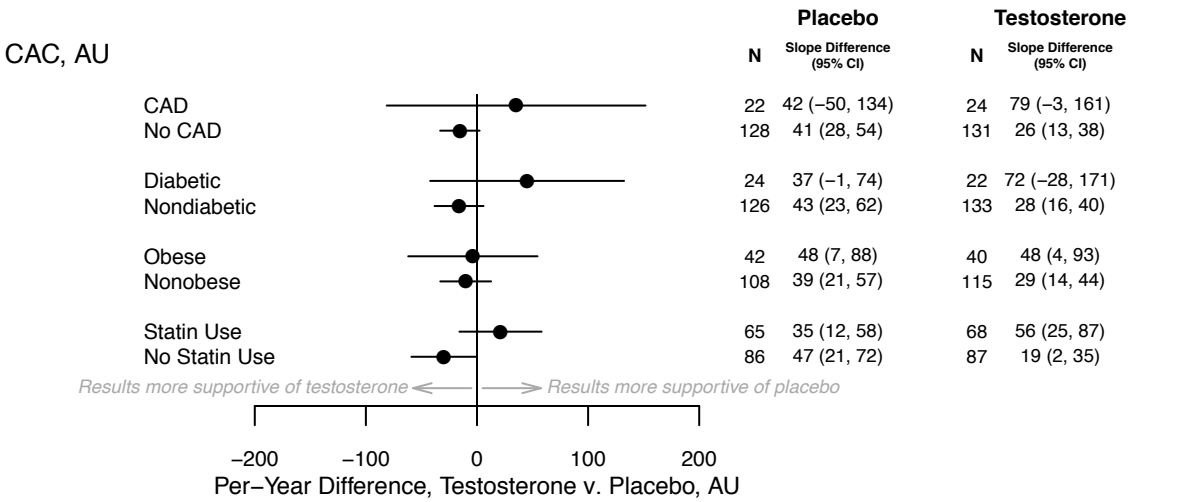


Baseline and on−treatment health−related quality of life data acquired using the MOS 36−item short−form health survey (SF−36), summarized by domain and overall score.

Data on the full SF−36 were obtained at the Charles R. Drew University and Boston University centers. Sample means and 95% confidence intervals shown for each visit and arm are based on observed data. Model−based estimates of on−treatment difference between arms, controlling for age group and study center, and accommodating missing records via multiple imputation, are provided on each panel in italicized text. Number of observed data points at each visit is provided along the horizontal axis.

Supplementary Figure 6





Exploratory subgroup analyses of testosterone effects by participant subcategories of men who had coronary artery disease (CAD) or diabetes, or who were obese or statin users at baseline.

The per−year intervention effect (the estimated difference between the testosterone and placebo groups in per−year change in CCA−IMT and CAC) in each subgroup is shown along with the accompanying 95% confidence interval. The point estimates to the left of zero indicate that randomization to the testosterone arm was associated with lower rates of subclinical atherosclerosis progression than randomization to the placebo arm, and the point estimates to the right of zero indicate that randomization to testosterone was associated with greater rates of atherosclerosis progression than randomization to placebo. In the right margins, annotations provide point and 95% confidence interval estimates of per−year change derived from analyses restricted to placebo and testosterone arms. All estimates were derived from mixed−effects regression models controlling for age group and study center, and estimated using observed data (see Methods).