ENDOGENOUS SERUM TESTOSTERONE IN MAN: AGEING, THE METABOLIC SYNDROME, FUNCTIONAL DECLINE AND THE ROLE OF SUPPLEMENTATION

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CHAPTER 5

5.1 THE ASSOCIATIONS OF TOTAL, BIOAVAILABLE AND FREE TESTOSTERONE AND SHBG WITH SOCIO-DEMOGRAPHICS, DISEASE RISK FACTORS AND BEHAVIOURS, CHRONIC DISEASE AND MEDICATION USE.

SUMMARY

This chapter investigates socio-demographic, disease risk factor and behaviour; chronic disease and medication associations with respect to total testosterone, measured and calculated bioavailable testosterone, calculated free testosterone and SHBG. Data were from the FAMAS as described in Chapter 4.0. Age was the common independent predictor of all measured serum testosterone and SHBG concentrations. Marriage, whether past or present, appeared to relate to both lower total and biologically available pools of testosterone in serum. Higher abdominal obesity, being a non-smoker and taking medications for general and endocrine, metabolic and nutritional disease was strongly associated with lower total and free testosterone levels. Lower alcohol intake was associated with lower BT levels. Metabolic, endocrine and nutritional conditions, including hypercholesterolaemia, were also associated with higher SHBG levels. Low total and free testosterone and possibly higher SHBG levels appear to be potential markers of the metabolic syndrome. Being aged 60 or older is the most discriminative predictor of low BT in men. Abdominal obesity, high serum triglycerides, high HbA1c and being a non-smoker better predict men with low total T.

INTRODUCTION

As stated previously, the optimal method for determining plasma testosterone levels is not clear [13, 109, 223]. In men, plasma testosterone has been shown to progressively decline, beginning around the third decade of life in both cross-sectional [54, 57, 58, 59, 71, 72, 74, 224-226] and longitudinal studies [24, 35, 47, 67, 227]. The mechanisms that may be responsible for this include age-related changes to the hypothalamic-pituitary-testicular axis, increased SHBG levels, lifestyle and behavioural factors, medication and chronic disease [24, 72]. Physical activity does not appear to be associated with serum testosterone or SHBG levels [228] [53] [229]. Serum total and free testosterone and SHBG but not bioavailable testosterone have been reported to be positively associated with smoking in a longitudinal [230] and several cross-sectional or case-control studies [58, 69, 231, 232]. However, total, bioavailable and free testosterone levels did not differ between smokers and non-smokers in two well-design, population-based, cross-sectional studies [27, 233]. Various studies report on associations between smoking and adrenal hormones, but these are beyond the scope of this chapter.

Reported associations between testosterone levels and alcohol intake are varied in the current literature. A small but significant increase in testosterone with alcohol consumption was reported in older men [71] and inverse associations between alcohol intake and the free testosterone index [67] and total testosterone [232] have been reported. SHBG has been shown to be both positively [232] and inversely [234] associated with alcohol intake in two separate cross-sectional studies in Japan. A number of studies report no significant associations of alcohol intake with serum testosterone and SHBG levels [27, 58, 229, 235].

Very few studies reported on associations between serum testosterone levels and dietary energy and macronutrient intake. Nagata et al. (1990) reported an inverse association between total fat intake and SHBG levels and a trend towards an inverse association with total but not free testosterone [234]. Massachusetts Male Ageing Study data showed an inverse association between SHBG and intake of animal fat [58].

Positive associations between HDL cholesterol and total and free testosterone [101, 106] and negative associations between HDL cholesterol and SHBG levels have been reported in some but not all studies[102, 106]. Inverse relationships between total serum triglycerides and total testosterone have been found [103, 104]. In a cross-sectional study, Simon et al. (1997) reported that men with lower total T (<10 nmol/L) had significantly higher total and LDL cholesterol and lower HDL cholesterol than men with higher total T, possibly as a result of the increase in visceral adiposity seen in men with low testosterone levels [105].

In a longitudinal analysis of 66 male, Multiple Risk Factor Intervention Trial participants aged 41-61 years, the decline in testosterone levels at the 13 year follow-up, after controlling for obesity and other lifestyle covariates, was associated with both increased triglycerides and decreased HDL, but not with changes in total or LDL cholesterol [47].

Men with impaired fasting glucose levels, impaired glucose tolerance or Type 2 diabetes have been shown to have significantly lower total testosterone levels than men with normal glucose tolerance [236]. Moreover, the same authors reported a significant inverse linear association between total testosterone and fasting serum glucose [236]. Longitudinally, low levels of total testosterone but not bioavailable testosterone, were associated with increased risk of incident diabetes after controlling for baseline age, body mass index and SBP [237]. Similarly, Stellato et al. (2000) showed that mean total and free testosterone and SHBG levels were lower in men who subsequently developed diabetes [42].

Few studies have reported a direct association between serum testosterone levels and prostate cancer. Two prospective, population-based studies reported a lack of association between measures of serum testosterone and risk or presence of prostate cancer, although they did report relationships with androstenedione and androstenedione glucuronide [238] [20]. Numerous case-control studies have reported serum testosterone associations with incident and risk of prostate cancer [239] [240, 241] [107, 242]. Gann et al. (1996) reported an increase in risk of prostate cancer with increasing total testosterone and decreasing SHBG levels [107]. However, Nomura et al. (1998) reported a similar prostate cancer risk in men with total testosterone, free testosterone, dihydrotestosterone, 3-alpha-androstanediol glucuronide, androsterone glucuronide, and androstenedione and total testosterone:dihydrotestosterone ratios in the second and third tertiles [48]. Carter et al. (1995) reported that free testosterone levels were significantly higher in men subsequently diagnosed with prostate cancer 10 – 15 years later than those who remained cancer free [241]. In addition, an inverse association between prostate volume and SHBG has been reported, but not with any measure of androgens other than androstenediol glucoronide [243] and Gann et al. (1995) reported an absence of association between serum androgen levels and risk of surgically treated benign prostatic hyperplasia [244].

Studies reporting on associations between specific types of medications and serum testosterone levels are greatly lacking. Harman et al. (2001) did however, report higher free testosterone index in beta-blocker users as compared to non-users [67]. Other studies have reported inverse associations between the number of current medications used and dehydroepiandosterone sulphate (DHEAS) levels, but these associations are beyond the scope of this chapter.

In this chapter, associations of serum testosterone and SHBG levels with socio-demographics, disease risk factors and behaviours, chronic disease and types of medication currently used are investigated.

MATERIALS AND METHODS

PARTICIPANT SELECTION

Participants were male volunteers (N = 568), living in the North and West suburbs of Adelaide and recruited at random from the EWP's as described in Chapter 4.0.

MEASUREMENTS

All assessments were performed according to the methods described in Chapter 4.0. Specifically, morning blood samples were obtained and assayed for total T and SHBG and FT was calculated, as described in Chapter 4.0. BT was measured and cBT calculated as described in Chapter 3.0. Cigarette smoking, exercise and alcohol intake and the daily dietary intake of energy, fat, carbohydrate and protein were assessed by questionnaire as described in Chapter 4.0. Chronic disease included but was not limited to depression, diabetes, hypertension, hypercholesterolaemia, BPH, and prostate cancer and current medications were determined by self-report. History of surgical procedures including prostatectomy, trans-urethral resection of prostate (TURP) and other urogenital surgery was obtained by questionnaire as described in Chapter 4.0.

STATISTICAL ANALYSIS

Initially, bivariate associations with serum testosterone and SHBG levels were investigated. For categorical data including demographics, chronic disease, urogenital surgery and medication use, mean serum testosterone and SHBG concentrations were compared using a Wald test of significance. In these cases, data presented are means ± S.E. with associated 95% confidence intervals and comparative F and P statistics. Associations between continuous variables including SBP, waist

circumference, cholesterol levels and other risk factor data, were determined by simple linear regression analysis, where data are presented as regression coefficients and associated 95% confidence intervals and R^2 and P statistics.

All associations were then adjusted for age linear regression with age as a continuous variable.

Multiple linear regression analysis was then used to determine independent factors associated with the different measures of serum T and SHBG. Criteria for inclusion in these models were association to the testosterone measure of interest or SHBG independent of age at a level of $P < 0.05$. For multiple linear regression analysis the regression coefficient and 95% confidence intervals (CI's) are reported. Post-hoc, chi-squared analyses were performed to assess the ability of the significantly associated factors to discriminate between low total T (< 8 nmol/L and < 12 nmol/L) and BT (< 3.1 nmol/L). All analyses were performed on stratified and probability weighted data as described in Chapter 4.0.

RESULTS

DEMOGRAPHICS

Serum total, bioavailable, calculated bioavailable, and free testosterone and SHBG levels (Appendix IV: Tables IV.I – IV.V) are reported in non-age adjusted analyses, by age, school-leaving age, highest post-secondary qualification, annual gross household income and work status, receipt of a DSS pension, marital status and country of birth All measures of testosterone concentration declined with increasing age, whilst SHBG increased and all measures related to each other (Figure 5.1.1).

In age-adjusted analyses marital status (married/living with partner > separated/divorced > widowed > never married) was positively associated with all measures of serum testosterone except for cBT. It was not associated with SHBG. Gross annual household income was inversely associated with both total T and SHBG and men who received a DSS pension had lower total T than those who did not (Table 5.1.1).

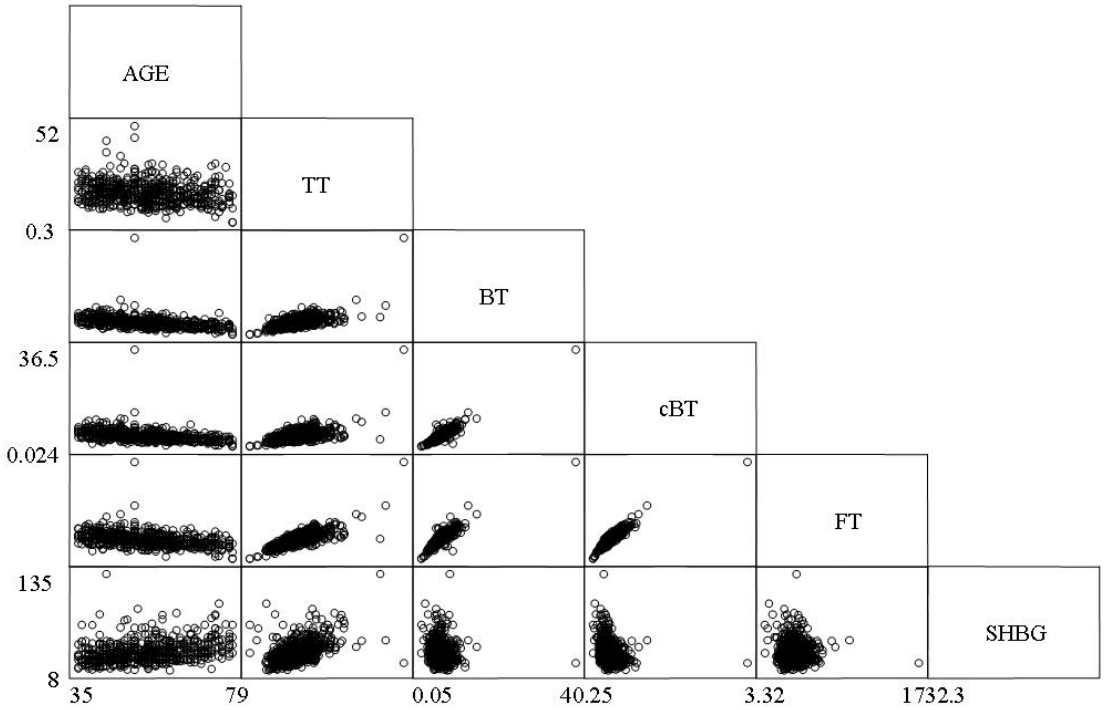

Figure 5.1.1 The associations between total T, BT, cBT, FT, SHBG and age.

TT is total T, BT bioavailable testosterone, cBT calculated bioavailable testosterone, FT calculated free testosterone, SHBG sex hormone binding globulin.

	Total T	
	Coeff (95% CI)	P
Age	-0.09 (-0.14 - -0.04)	0.0001
Household income	-0.45 (-0.86 - -0.03)	0.034
DSS pension	-2.23 (-3.91 - -0.54)	0.01
Marital status	1.13 (0.39 - 1.87)	0.003
	BT	
Age	-0.09 (-0.10 - -0.08)	<0.0001
Marital status	0.30 (0.12 - 0.49)	0.002
	cBT	
Age	-0.08 (-0.09 - -0.07)	<0.0001
	FT	
Age	-4.35 (-5.16 - -3.57)	<0.0001
Marital status	17.89 (4.85 - 30.92)	0.007
	SHBG	
Age	0.41 (0.30 - 0.52)	<0.0001
Household income	-1.10 (-2.00 - -0.20)	0.016

Table 5.1.1 Statistically significant age-adjusted associations between serum testosterone and SHBG levels and demographic variables

in 568 men recruited from randomly selected households in North-west Adelaide. Data presented are regression coefficients with 95% confidence intervals and P values weighted by age and geographical location as described in Chapter 4.0.

PITUITARY HORMONES

In non-age-adjusted analyses, BT, cBT and FT were inversely related and SHBG was positively related to serum LH concentration. Total T was not related to serum LH concentration (Appendix IV Table IV.VI). All measures of testosterone were inversely related and SHBG was positively related to serum FSH concentration (Appendix IV Table IV.VI). Age-adjusted associations are shown in Table 5.1.2. SHBG, but no measure of serum testosterone, was positively associated with serum LH. BT, cBT and FT but not total T were inversely and SHBG was positively associated with serum FSH.

CHRONIC DISEASE RISK FACTORS AND BEHAVIOURS

The following data are adjusted for age.

Blood pressure

Systolic blood pressure was significantly and inversely associated with serum total T (Figure 5.1.2) but not to any other measure of serum testosterone or SHBG. Diastolic blood pressure was inversely associated with total T and SHBG (Figure 5.1.2) but not to BT, cBT or FT.

Waist circumference

Waist circumference was significantly inversely associated with all measures of serum testosterone and SHBG (Figure 5.1.3).

	Total T	
	Coeff (95% CI)	P
LH	-	-
FSH	-	-
	BT	
LH	-	-
FSH	-0.028 (-0.05 - -0.007)	0.011
	cBT	
LH	-	-
FSH	-0.023 (-0.042 - -0.004)	0.017
	FT	
LH	-	-
FSH	-1.676 (-3.112 - -0.239)	0.022
	SHBG	
LH	0.795 (0.402 - 1.189)	<0.0001
FSH	0.435 (0.189 - 0.682)	0.001

Table 5.1.2 Statistically significant age-adjusted associations between serum testosterone and SHBG levels and the serum levels of LH and FSH

in 568 men recruited from randomly selected households in North-west Adelaide. Data presented are regression coefficients with 95% confidence intervals and P values from weighted by geographical region and age as described in Chapter 4.0.

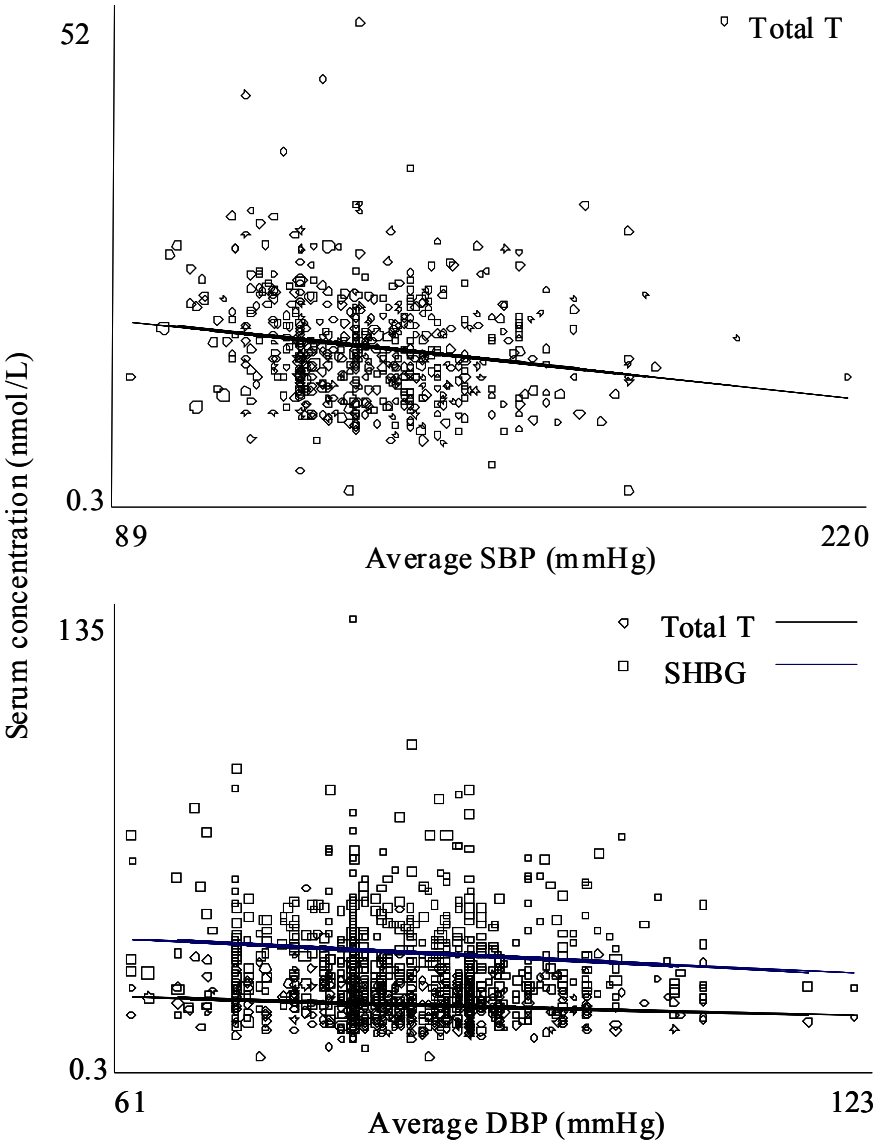

Figure 5.1.2 Age-adjusted associations of serum total T with systolic blood pressure (top panel) and of serum total T and SHBG with diastolic blood pressure (bottom panel) in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide.

SBP: Total T [Coeff. = -0.042 (95% CI -0.08 - -0.003), P = 0.036], DBP: Total T [Coeff. = -0.083 (-0.143 - -0.023) P = 0.007], SHBG [Coeff. = -0.229 (-0.364 - -0.093) P = 0.001). Data shown are weighted based on geographical region and age as described in Chapter 4.0. Size of data points is proportional to their weight.

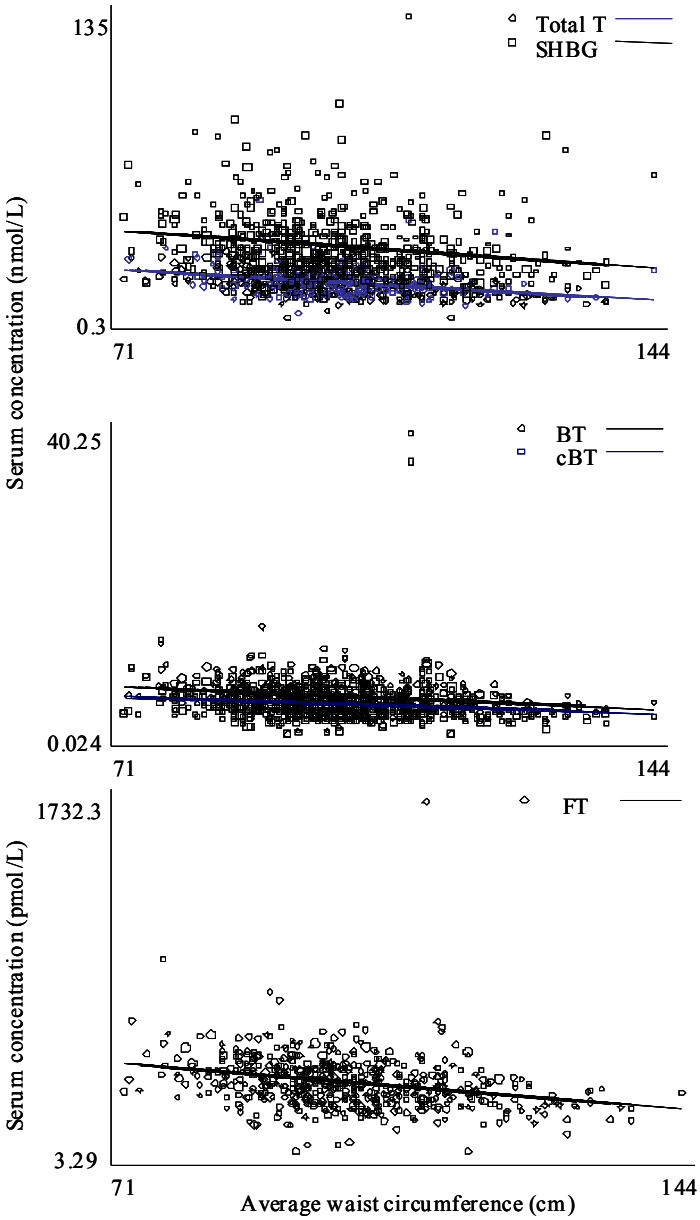

Figure 5.1.3 Age-adjusted associations of serum total T and SHBG (top panel), BT and cBT (middle panel) and FT (bottom panel) with waist circumference in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide.

Total T [Coeff. = -0.18 (-0.221 - -0.139) P < 0.0001), BT [Coeff. = -0.029 (-0.044 - -0.013) P < 0.0001], cBT [Coeff. = -0.021 (-0.035 - -0.006) P = 0.006], FT [Coeff. = -2.58 (-3.42 - -1.74) P < 0.0001], SHBG [Coeff. = -0.29 (-0.4 - -0.179) P < 0.0001]. Data shown are weighted based on geographical region and age as described in Chapter 4.0. Size of data points is proportional to their weight.

Serum lipids

Serum triglyceride levels were inversely associated with total T, FT and SHBG (Figure 5.1.4) but not to either BT or cBT. Total cholesterol was inversely, and HDL cholesterol was positively associated with total T and SHBG (Figure 5.1.5) but not to BT, cBT or FT.

Dietary total energy and macronutrient intake

Energy intake was inversely associated with total T, cBT and FT (Table 5.1.3) but not with BT or SHBG. Daily fat and protein intakes were inversely associated with total T and FT (Table 5.1.3) but not with BT, cBT or SHBG. Daily carbohydrate intake was inversely associated with cBT and FT (Table 5.1.3) but not with total T, BT or SHBG.

Glucose metabolism

Fasting serum glucose was inversely associated with all measures of serum testosterone and SHBG (Table 5.1.4). HbA1c levels were inversely associated with all measures of serum testosterone but not with SHBG (Table 5.1.4). Fasting serum insulin levels were inversely associated with total T, FT and SHBG, but not with BT or cBT (Table 5.1.4).

Daily alcohol intake

Daily alcohol intake was positively associated with BT (Coeff. = 0.014 (95% CI 0.005 – 0.023), P = 0.002) but not with any other measure of serum testosterone or SHBG.

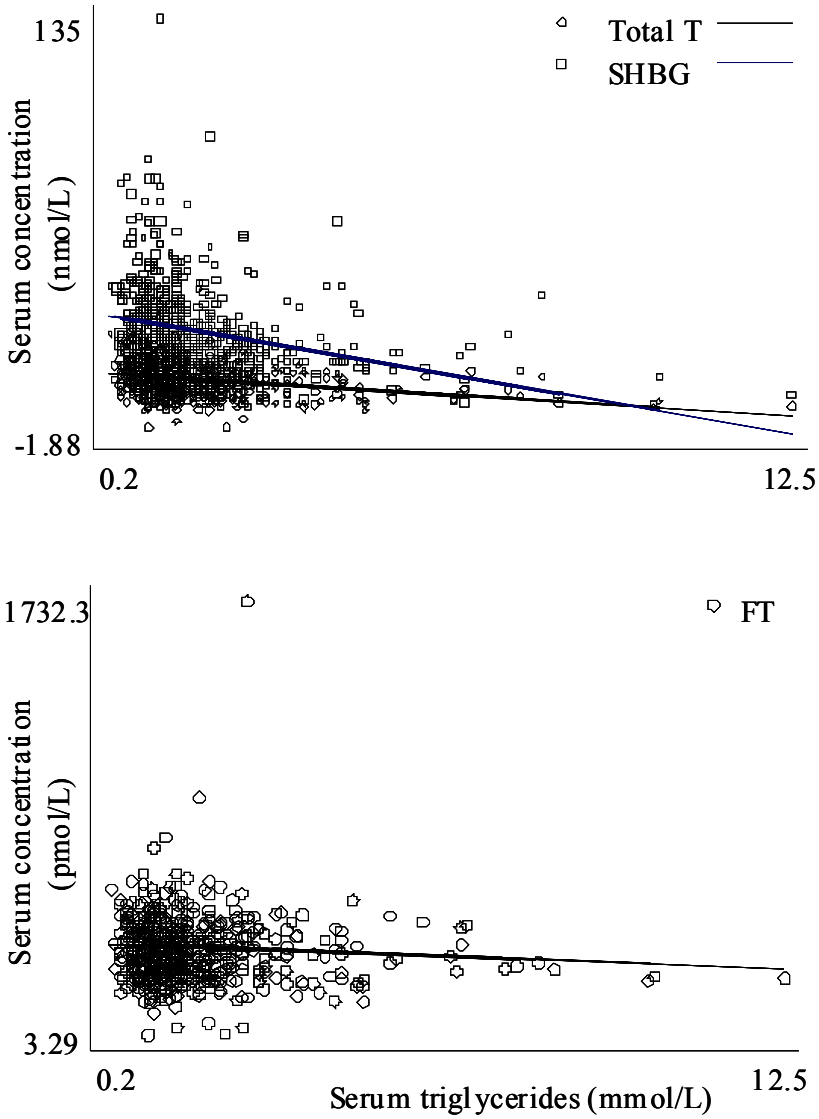

Figure 5.1.4 Age-adjusted associations of serum total T and SHBG (top panel) and FT (bottom panel) with serum triglycerides in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide.

Total T [Coeff. = -1.14 (-1.42 - -0.87) P < 0.0001], SHBG [Coeff. = -3.05 (-3.91 - -2.20) P < 0.0001], FT [Coeff. = -9.64 (-15.71 - -3.58) P = 0.002]. Data shown are weighted based on geographical region and age as described in Chapter 4.0. Size of data points is proportional to their weight.

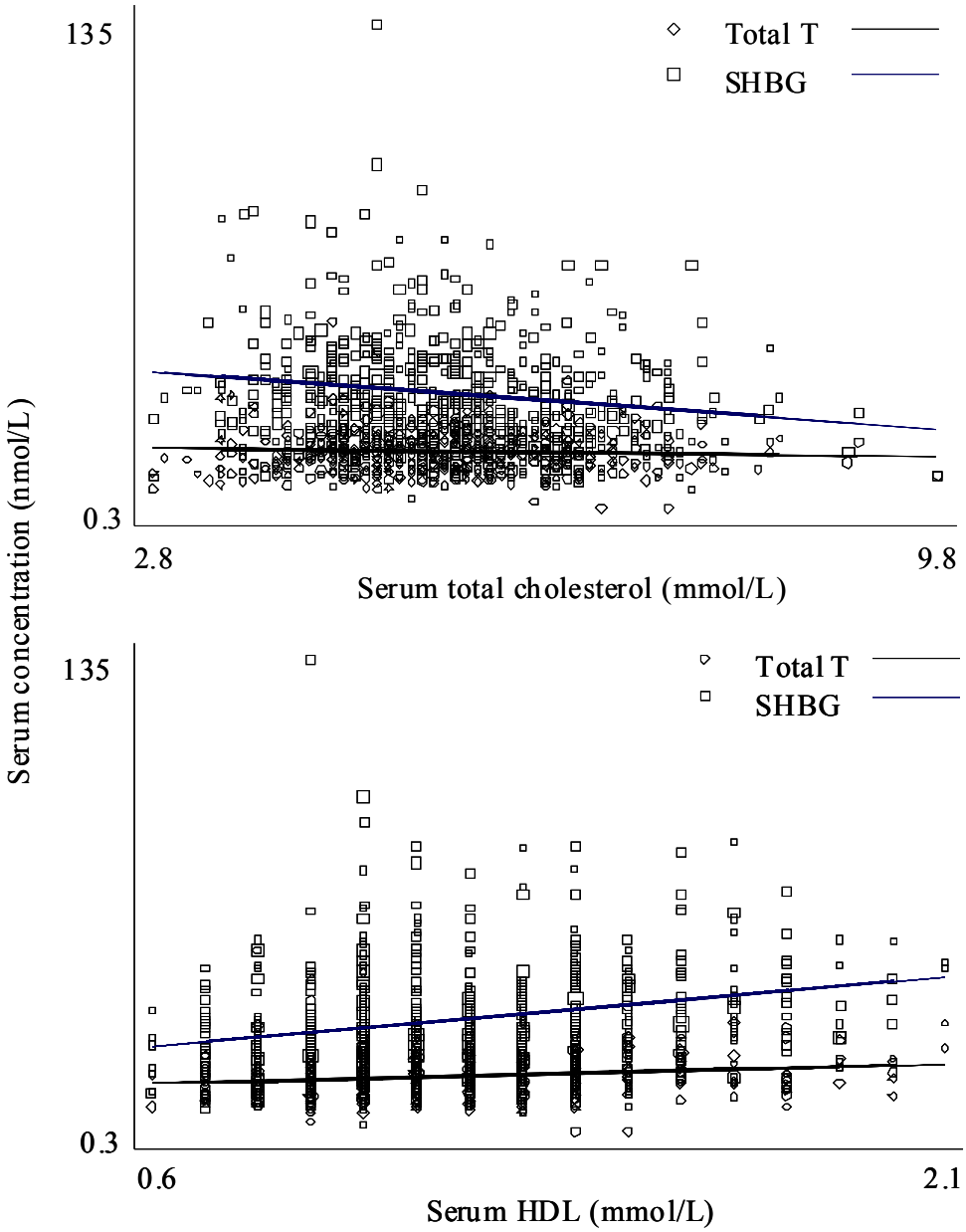

Figure 5.1.5 Age-adjusted associations of serum total T and SHBG with serum total cholesterol (top panel) and HDL cholesterol (bottom panel) in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide.

Total cholesterol: Total T [Coeff. = -0.63 (-1.13 - -0.13) P < 0.014], SHBG [Coeff. = -1.28 (-2.47 - -0.092) P < 0.035]. HDL cholesterol: Total T [Coeff. 4.33 (2.5 – 6.15) P < 0.0001], SHBG [Coeff. = 11.42 (7.64 – 15.20) P < 0.0001]. Data shown are weighted based on geographical region and age as described in Chapter 4.0. Size of data points is proportional to their weight.

	Total T		cBT		FT	
	Coeff. (95% CI)	P	Coeff. (95% CI)	P	Coeff. (95% CI)	P
Total energy (kJ)	-0.0002 (-0.0003 - -0.00002)	0.031	-0.00006 (-0.001 - -0.000002)	0.044	-0.004 (-0.007 - -0.0005)	0.023
Fat (g)	-0.016 (-0.03 - -0.002)	0.025	-	-	-0.3 (-0.59 - -0.016)	0.039
Carbohydrate (g)	-	-	-0.002 (-0.004 - -0.0001)	0.036	-0.12 (-0.24 - -0.005)	0.041
Protein (g)	-0.014 (-0.027 - -0.001)	0.031	-	-	-0.287 (-0.54 - -0.03)	0.029

Table 5.1.3 Statistically significant age-adjusted associations of serum total T, cBT and FT with daily dietary intakes of total energy, fat, carbohydrate and protein in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Data shown are weighted based on geographical region and age as described in Chapter 4.0.

	Fasting glucose		HbA1c		Fasting insulin	
	Coeff. (95% CI)	P	Coeff. (95% CI)	P	Coeff. (95% CI)	P
Total T	-0.89 (-1.28 - -0.49)	<0.0001	-1.49 (-2.05 - -0.94)	<0.0001	-0.14 (-0.20 - -0.08)	<0.0001
BT	-0.22 (-0.38 - -0.06)	0.007	-0.34 (-0.50 - -0.18)	<0.0001	-	-
cBT	-0.19 (-0.33 - -0.05)	0.008	-0.31 (-0.45 - -0.16)	<0.0001	-	-
FT	-15.25 (-23.54 - -6.96)	<0.0001	-27.84 (-37.22 - -18.46)	<0.0001	-1.87 (-2.85 - 0.90)	<0.0001
SHBG	-1.28 (-2.12 - -0.43)	0.003	-	-	-0.26 (-0.39 - -0.13)	<0.0001

Table 5.1.4 Statistically significant age-adjusted associations of serum testosterone and SHBG levels with fasting serum glucose, HbA1c and fasting serum insulin in

568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Data shown are weighted based on geographical region and age as described in Chapter 4.0.

Physical activity

None of the measures of serum testosterone or SHBG were associated with being sedentary, insufficiently active, or sufficiently active enough to confer a health benefit.

Smoking

Current smoking was associated with higher levels on all measures of serum testosterone (Table 5.1.5). Current smoking was not associated with serum SHBG levels.

Chronic disease, surgical procedures and medications

The non-age-adjusted associations of chronic disease, surgical procedures and medication with serum testosterone and SHBG levels are shown in Appendix IV (Tables IV.VII – IV.XI). In age-adjusted analyses, lower levels of all measures of serum testosterone were associated with having diabetes (Figure 5.1.6). SHBG level was not associated with having diabetes. Lower serum levels of both total T and SHBG were associated with hypercholesterolaemia and other metabolic, endocrine or nutritional health conditions (Figure 5.1.7); BT, cBT and FT were not. Lower serum total T, but not any other measure of serum testosterone or SHBG, was associated with hypertension [Coeff. -1.37 (95% CI -2.54 to -0.19) P = 0.023] and higher total T with having a respiratory health condition [Coeff. 1.95 (0.46 to 3.88) P = 0.045]. Lower levels of both BT and cBT were associated with taking medications for general health conditions and additionally lower BT was associated with taking medications for urinary conditions (Figure 5.1.8). Lower cBT, but not any other measure of testosterone or SHBG was associated with having prostate cancer [Coeff. -0.73 (-1.43 to -0.027) P = 0.042]. Lower SHBG, but not any measure of serum testosterone, was associated with having angina and with taking medications for genital and metabolic, endocrine or nutritional health conditions (Figure 5.1.9).

	Coeff. (95% CI)	P
Total T	-2.37 (-3.60 - -1.14)	<0.0001
BT	-0.46 (-0.85 - -0.06)	0.022
cBT	-0.41 (-0.78 - -0.044)	0.028
FT	-38.32 (-61.93 - -14.71)	0.002

Table 5.1.5 Statistically significant age-adjusted associations of serum testosterone levels with current smoking

in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Current smoking is dichotomised to yes and no answers. An inverse association means current smokers have higher testosterone concentrations. Data shown are weighted based on geographical region and age as described in Chapter 4.0.

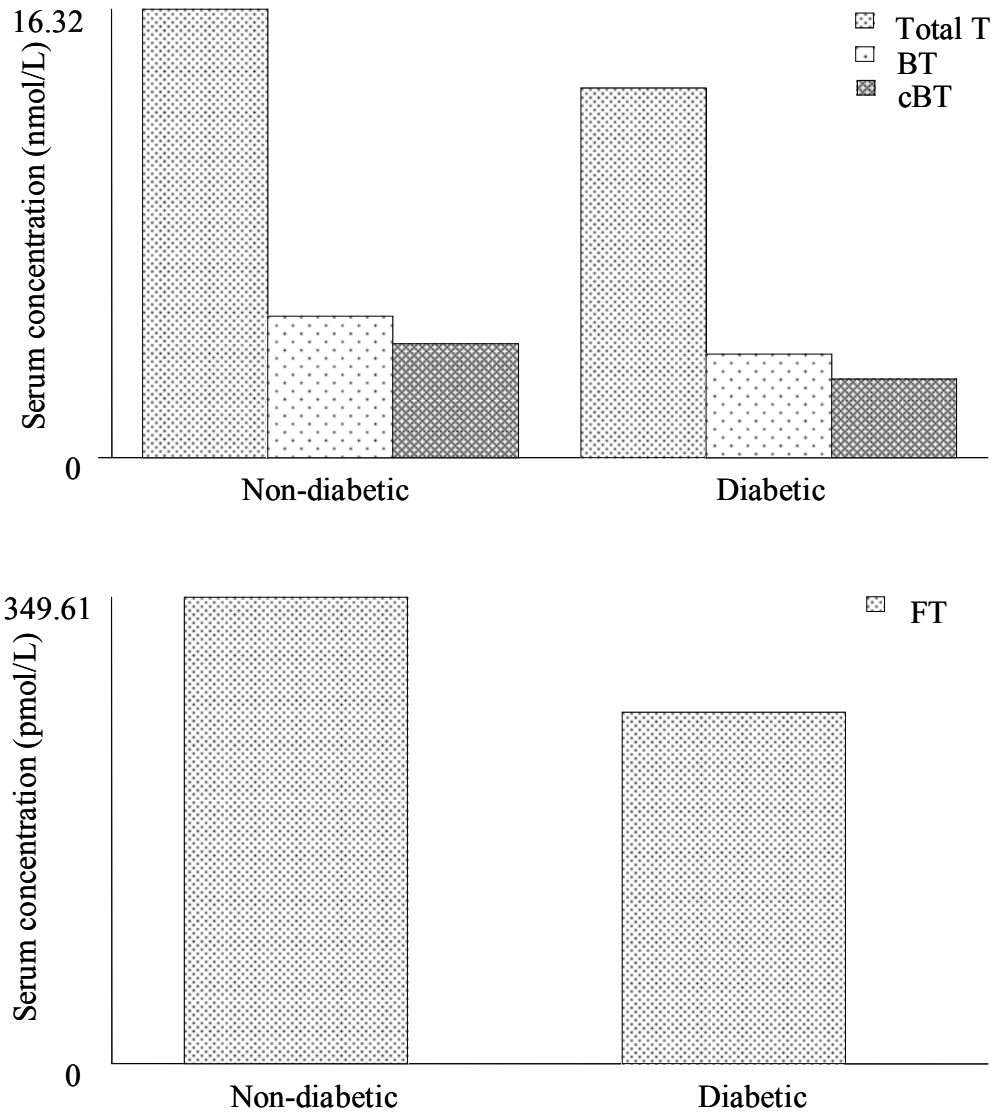

Figure 5.1.6 Age-adjusted associations of serum total T, BT and cBT (top panel) and FT (bottom panel) with diabetic status

in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Total T [Coeff. = -2.50 (-4.27 - -0.73) P < 0.006], BT [Coeff. = -0.59 (-1.06 - -0.11) P = 0.015], cBT [Coeff. = -0.53 (-1.0 – -0.06) P = 0.027], FT [Coeff. = -50.05 (-80.52 – -19.60) P = 0.001]. Data shown are weighted based on geographical region and age as described in Chapter 4.0.

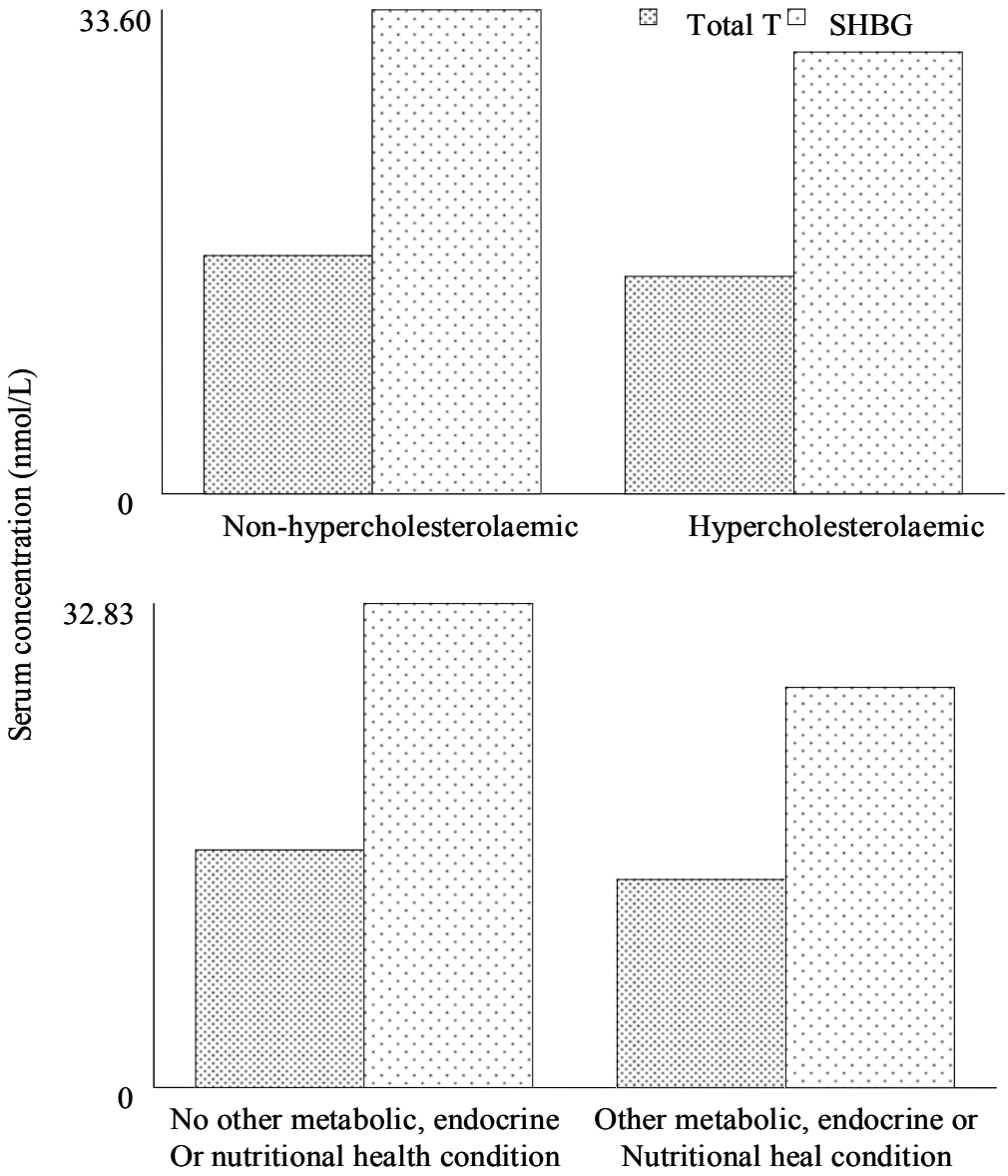

Figure 5.1.7 Age-adjusted associations of serum total T and SHBG with cholesterolaemia (top panel) and the other metabolic, endocrine or nutritional health conditions (bottom panel)

in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Cholesterolaemia: Total T [Coeff. = -1.19 (-2.35 - -0.03) P = 0.044], SHBG [Coeff. = -5.73 (-8.18 - -3.27) P < 0.0001]. Metabolic, endocrine or nutritional health condition: Total T [Coeff. = -2.16 (-4.21 – -0.12) P = 0.038], SHBG [Coeff. = -8.51 (-13.20 – -3.81) P < 0.0001]. Data shown are weighted based on geographical region and age as described in Chapter 4.0.

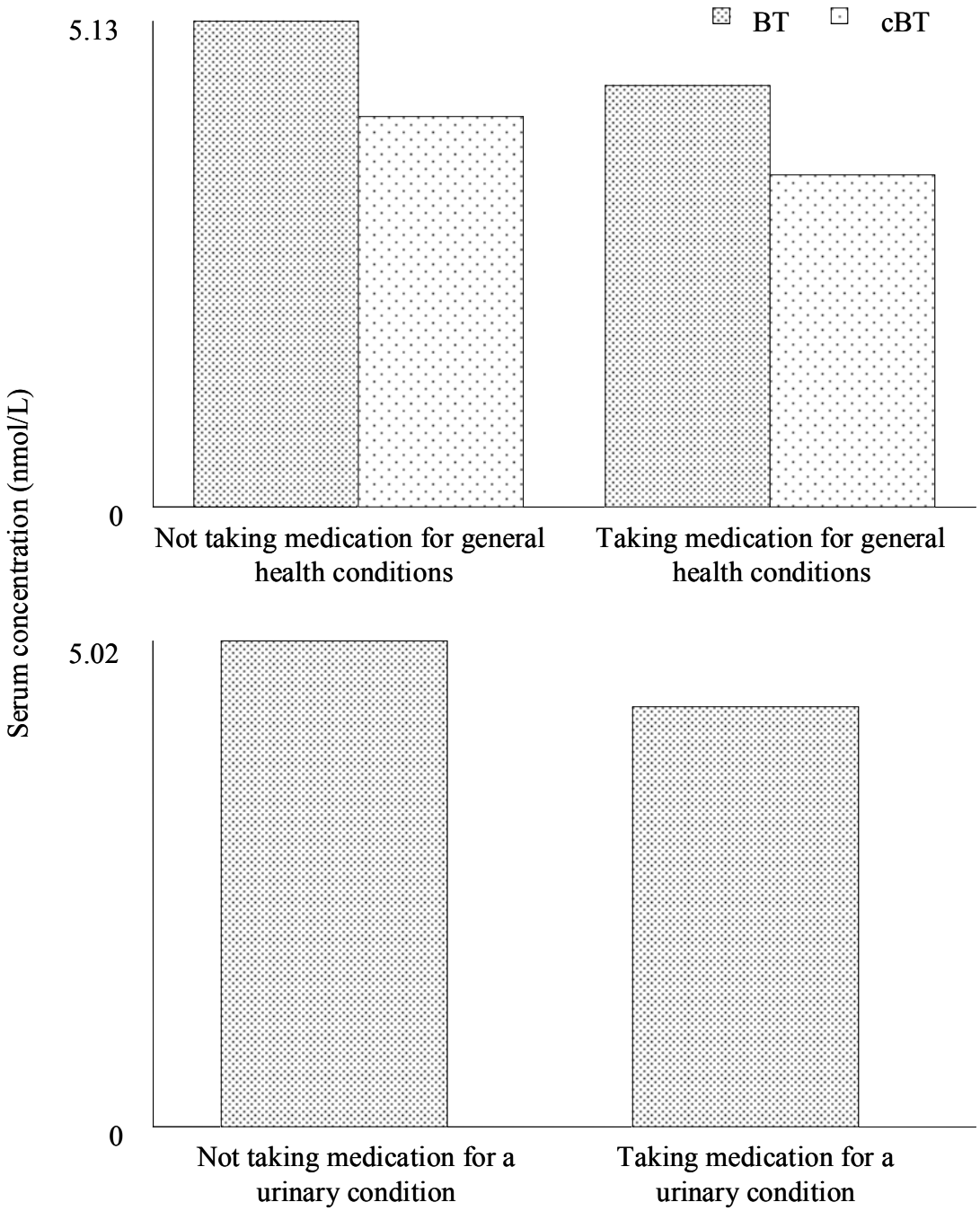

Figure 5.1.8 Age-adjusted associations of serum BT and cBT with general health condition medication (top panel) and of BT with medication for urinary health conditions (bottom panel)

in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Medication for general health: BT [Coeff. = -0.41 (-0.81 - -0.004) P = 0.048], cBT [Coeff. = -0.42 (-0.83 - -0.02) P = 0.042]. Medication for urinary conditions: BT [Coeff. = -0.87 (-1.69 – -0.06) P = 0.035]. Data shown are weighted based on geographical region and age as described in Chapter 4.0.

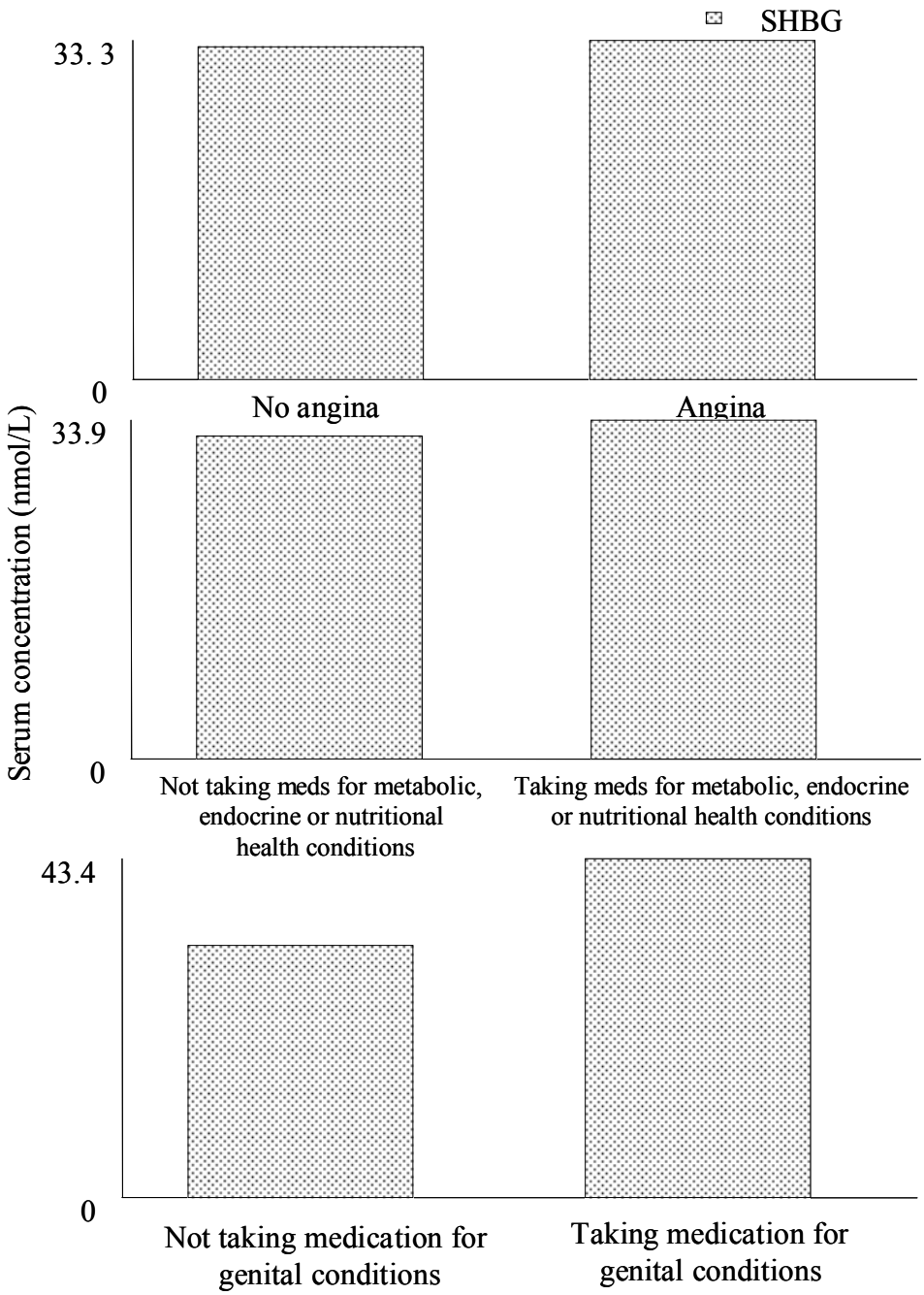

Figure 5.1.9 Age-adjusted associations of serum SHBG with angina (top panel), medication for metabolic, endocrine or nutritional health conditions (middle panel) and medication for genital conditions (bottom panel)

in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Angina: SHBG [Coeff. = -6.19 (-11.14 - -1.23) P = 0.014]; Medication for metabolic, endocrine or nutritional health conditions: SHBG [Coeff. = -3.81 (-7.14 - -0.47) P = 0.025]; Medication for genital conditions: SHBG [Coeff. = 7.47 (0.19 – 14.75) P = 0.044]. Data shown are weighted based on geographical region and age as described in Chapter 4.0.

MULTIVARIATE PREDICTIVE MODELS FOR SERUM TESTOSTERONE AND SHBG CONCENTRATIONS

Factors significantly associated with serum testosterone and SHBG levels after age-adjusted at a level of $P \leq 0.01$ were included in multiple regression predictive models.

Total testosterone

Being older ($P < 0.0001$), currently or formerly married ($P = 0.011$), having a larger waist circumference ($P < 0.0001$) and higher total serum triglycerides ($P = 0.007$), being a non-smoker ($P = 0.005$) and having higher HbA1c ($P = 0.014$) and lower SHBG ($P < 0.0001$) levels were all independently associated with lower total T levels (Table 5.1.6). The predicted values for total testosterone based on the independent predictors from the regression model are graphed against measured total testosterone values in Figure 5.1.10.

Bioavailable testosterone

Being older ($P < 0.0001$), currently or formerly married ($P = 0.006$), having a larger waist circumference ($P = 0.004$) and a lower daily intake of alcohol ($P = 0.007$) were all significantly and independently associated with lower BT levels (Table 5.1.7). The predicted values for BT based on the independent predictors from the regression model are graphed against measured BT values in Figure 5.1.11.

Calculated bioavailable testosterone

Being older ($P < 0.0001$) was the only independently significant factor associated with lower cBT levels. There was a trend toward an association between higher waist circumference and lower cBT (Table 5.1.8).

Free testosterone

Being older (P < 0.0001), currently or formerly married (P = 0.009), having a larger waist circumference (P < 0.0001), being a non- smoker (P = 0.002) and having a higher HbA1c (P = 0.026) were all significantly and independently associated with lower FT levels (Table 5.1.9).

Sex hormone binding globulin

Being younger (P < 0.0001), having higher serum triglycerides (P = 0.001), lower total T (P < 0.0001) and having hypercholesterolaemia (P = 0.001) and other metabolic, endocrine or nutritional health conditions (P = 0.033) were significantly and independently associated with higher SHBG levels (Table 5.1.10). The predicted values for SHBG based on the independent predictors from the regression model are graphed against measured SHBG values in Figure 5.1.12.

	Coeff.	S.E.	t	P	95% CI	
Age	-0.155	0.025	-6.31	0.000	-0.203	-0.107
Marital status	0.689	0.268	2.57	0.011	0.162	1.216
DSS pension	-0.943	0.709	-1.33	0.184	-2.335	0.448
DBP	0.018	0.024	0.76	0.449	-0.029	0.065
Waist circumference	-0.101	0.022	-4.52	0.000	-0.145	-0.057
Serum triglycerides	-0.366	0.136	-2169	0.007	-0.633	-0.099
HDL	-0.363	0.841	-0.43	0.666	-2.014	1.288
Fasting glucose	0.197	0.255	0.77	0.440	-0.305	0.699
HbA1c	-0.874	0.354	-2.47	0.014	-1.570	-0.178
Fasting insulin	-0.010	0.022	-0.46	0.646	-0.053	0.033
Current smoking	-1.521	0.538	-2.83	0.005	-2.577	-0.464
SHBG	0.198	0.026	7.48	0.000	0.146	0.250
Diabetes	-0.716	0.884	-0.81	0.419	-2.453	1.021

Table 5.1.6 A predictive model for serum total T concentration.

The model was significantly predictive of total T levels ($F(13, 551) = 28.10$, $P < 0.0001$, $R2 = 0.43$.

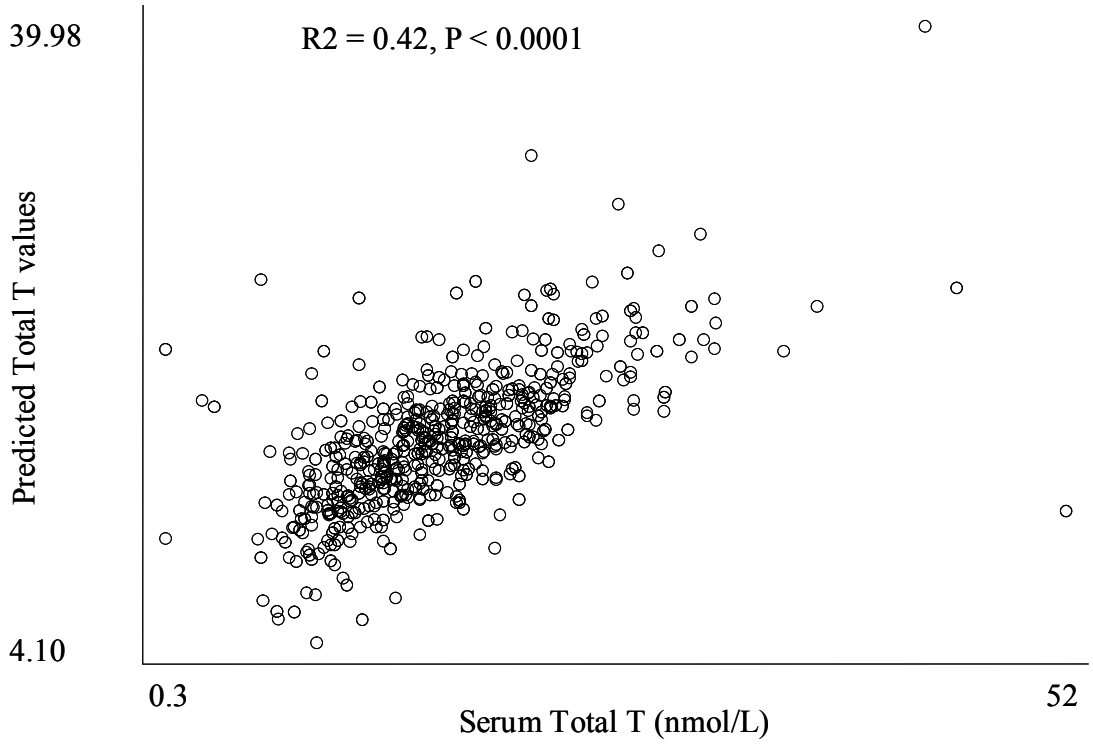

Figure 5.1.10 Regression predicted values for total T versus measured serum total T

in 568 men aged 35 – 80 years from randomly selected households in the North-west of Adelaide. Predicted values represent the combination of independently associated factors (age, marital status, waist circumference, triglycerides, SHBG, HbA1c and current smoking status). Data presented are weighted for geographical sampling region and age as described in Chapter 4.0. Data point sizes represent the weight of the data points in the model.

	Coeff.	S.E.	t	P	95% CI	
Age	-0.078	0.006	-12.37	0.000	-0.090	-0.065
Marital status	0.281	0.102	2.77	0.006	0.082	0.481
Waist circumference	-0.025	0.009	-2.85	0.004	-0.041	-0.008
Alcohol intake	0.013	0.005	2.69	0.007	0.004	0.0236
Fasting glucose	-0.118	0.147	-0.80	0.423	-0.406	0.171
HbAIc	-0.109	0.155	-0.709	0.482	-0.413	0.195

Table 5.1.7 A predictive model for serum BT concentration.

The model was significantly predictive of BT levels ($F(6, 559) = 49.83$, $P < 0.0001$, $R2 = 0.24$.

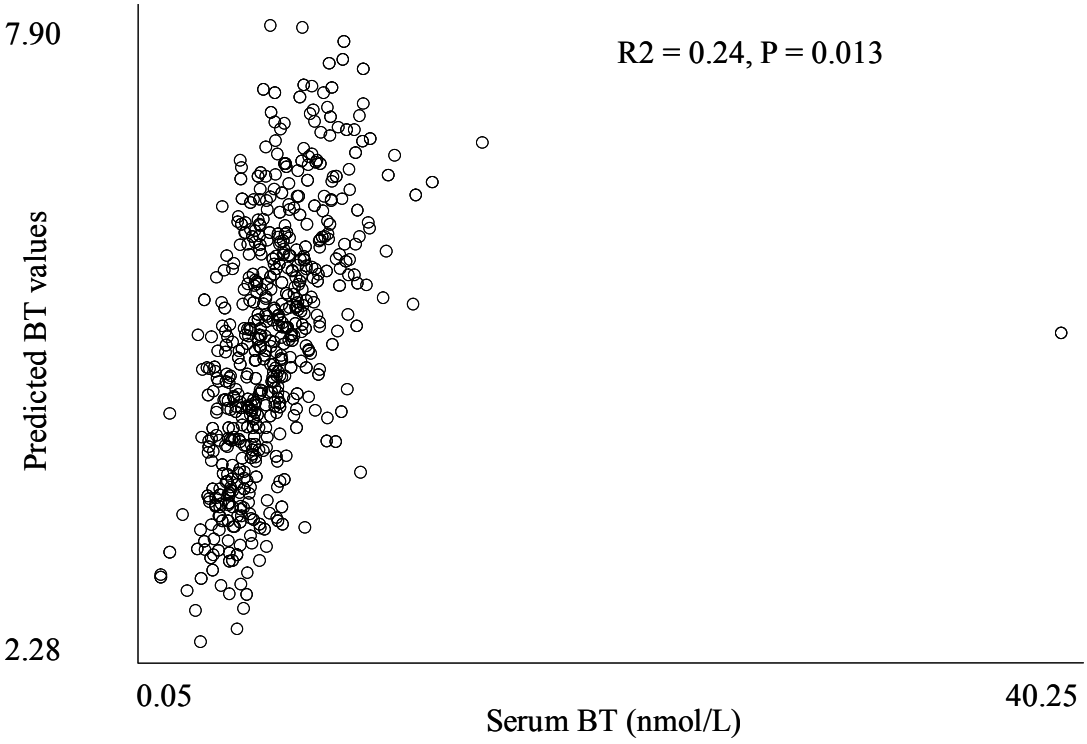

Figure 5.1.11 Regression predicted values for BT versus measured serum BT

in 568 men aged 35 – 80 years from randomly selected households in the North-west of Adelaide. Predicted values represent the combination of independently associated factors (age, marital status, waist circumference, and alcohol intake). Data presented are weighted for geographical sampling region and age as described in Chapter 4.0. Data point sizes represent the weight of the data points in the model.

	Coeff.	S.E.	t	P	95% CI	
Age	-0.072	0.005	-13.12	0.000	-0.082	-0.061
Waist circumference	-0.017	0.009	-1.92	0.056	-0.034	-0.0004
Fasting glucose	-0. 054	0.139	-0.39	0.698	-0.326	0.289
HbA1c	-0.184	0.153	-1.20	0.230	-0.48	0.117

Table 5.1.8 A predictive model for cBT concentration.

The model was significantly predictive of cBT levels ($F(4, 561) = 57.57$, $P < 0.0001$, $R2 = 0.19$.

	Coeff.	S.E.	t	P	95% CI	
Age	-3.496	0.401	-8.72	0.000	-4.283	-2.708
Marital status	17.203	6.523	2.64	0.009	4.390	30.017
Waist circumference	-2.073	0.486	-4.26	0.000	-3.078	-1.117
Current smoking	-35.442	11.575	-3.06	0.002	-58.178	-12.706
Fasting glucose	1.754	6.989	0.25	0.802	-11.972	15.480
HbA1c	-18.889	8.479	-2.23	0.026	-35.543	-2.235
Fasting insulin	-0.094	0.551	-0.17	0.864	-1.176	0.987
Diabetes	-13.414	16.601	-0.81	0.419	-46.021	19.194
Fasting triglycerides	-4.706	3.041	-1.55	0.122	-10.679	1.268

Table 5.1.9 A predictive model for FT concentration.

The model was significantly predictive of FT levels ($F(9, 555) = 24.23$, $P < 0.0001$, $R2 = 0.26$.

	Coeff.	S.E.	t	P	95% CI	
Age	0.4288	0.044	9.66	0.000	0.341	0.515
DBP	-0.062	0.054	-1.16	0.248	-0.168	0.043
Waist circumference	0.014	0.067	0.21	0.830	-0.117	0.145
HDL	3.585	2.071	1.73	0.084	-0.483	7.654
Serum total T	1.158	0.209	5.55	0.000	0.748	1.568
FSH	0.276	0.152	1.81	0.071	-0.024	0.575
LH	0.413	0.308	1.34	0.181	-0.192	1.018
Metabolic, endo, nut health condition	-3.863	1.809	-2.14	0.033	-7.416	-0.310
Fasting glucose	0.299	0.387	0.77	0.440	-0.461	1.509
Fasting insulin	-0.029	0.050	-0.58	0.564	-0.128	0.070
Fasting triglycerides	-1.341	0.391	-3.43	0.001	-2.110	-0.573
Hypercholesterolaemia	-3.606	1.074	-3.36	0.001	-5.716	-1.496

Table 5.1.10 A predictive model for SHBG concentration.

The model was significantly predictive of SHBG levels ($F(12, 552) = 34.30$, $P < 0.0001$, $R2 = 0.49$.

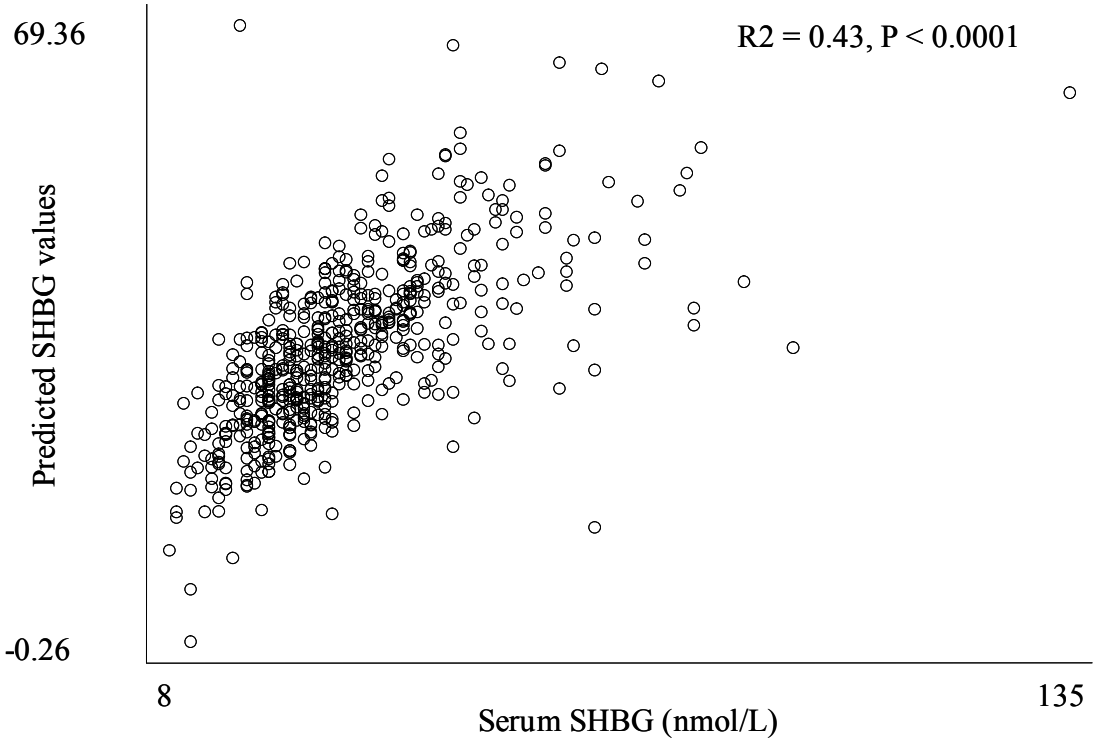

Figure 5.1.12 Regression predicted values for SHBG versus measured serum SHBG

in 568 men aged 35 – 80 years from randomly selected households in the North-west of Adelaide. Predicted values represent the combination of independently associated factors (age, serum total T, triglycerides, and self-reported high cholesterol and other metabolic, endocrine or nutritional health conditions). Data presented are weighted for geographical sampling region and age as described in Chapter 4.0. Data point sizes represent the weight of the data points in the model.

DO THE SIGNIFICANTLY ASSOCIATED FACTORS PREDICT LOW TESTOSTERONE LEVELS?

Post-hoc, chi-squared analyses were performed to assess the ability of the significantly associated factors to discriminate between low total T (< 8 nmol/L and < 12 nmol/L) and BT (< 3.1 nmol/L). All 2 x 2 tables are shown in Appendix IV (Chi-squared tables).

Discriminators of BT < 3.1 nmol/L

Being aged 60 or older was the best discriminator, accounting for 38% of low BT (Chi2 = 83.3, P < 0.0001, phi = 0.38). Having a waist circumference of greater than 102 cm, accounted for 17% of discriminatory power (Chi2 = 17.3, P < 0.0001, phi = 0.17). Addition of the two factors added no further discriminatory power. Serum triglycerides (> 2 mmol/L) and daily alcohol intake in the 75th (31.92 g, approx 3 standard drinks) and 90th percentiles (49.93 g, approx 5 standard drinks) did not discriminate for low BT.

Discriminators of total T < 8 nmol/L

Having an HbA1c ≥ 6.2% was the strongest discriminator, accounting for 19% of total T < 8 nmol/L (Chi2 = 19.91, P < 0.0001, phi = 0.19). Having a waist circumference greater than 102 cm had 16% discriminatory power (Chi2 = 14.8, P < 0.0001, phi = 0.16) and being aged 60 or older accounted for 14% of the discriminatory power (Chi2 = 11.11, P = 0.0009, phi = 0.14). Serum triglycerides greater than 2 mmol/L had 11% discriminatory power (Chi2 = 6.48, P = 0.013, phi = 0.11). Being 60 years or older and having serum triglycerides greater than 2 mmol/L had 26% discriminatory power (Chi2 = 29.19, P < 0.0001, phi 0.26). The addition of any other factors failed to improve discriminatory power.

Discriminators of total T < 12 nmol/L

Being aged 60 years or older (Chi2 = 21.11, P < 0.0001, phi = 0.19), having a waist circumference greater than 102 cm (Chi2 = 20.6, P < 0.0001, phi = 0.19), HbA1c ≥ 6.2% (Chi2 = 25.51, P < 0.0001, phi = 0.21) and being a non-smoker (Chi2 = 25.39, P < 0.0001, phi = 0.21) had similar discriminatory power for total T less than 12 nmol/L (19% – 21%). Serum triglycerides greater than 2 mmol/L alone, was marginally less discriminative (Chi2 = 13.43, P = 0.0006, phi = 0.15), but when in association with being 60 years or older discrimination was 26% (Chi2 = 29.19, P < 0.0001, phi 0.26). The best discriminator of total T < 12 nmol/L was being a non-smoker with a waist circumference greater than 102 cm and fasting serum triglycerides greater than 2 mmol/L (Chi2 = 43.8, P < 0.0001, phi = 0.28). The combination of any other number of factors added no further discriminatory power.

DISCUSSION

A major aim of this chapter was to identify the major predictors of testosterone and SHBG levels in serum. Marriage, whether past or present, appeared to relate to both lower total and biologically available pools of testosterone in serum. This finding may be a product of recruitment bias. As was indicated in Chapter 4.0, the cohort was under-represented by younger men who had never married. However, this bias is more likely to underestimate the effect of not being married on serum testosterone levels. Although statistical weighting gave younger men's data greater influence in an attempt to counter the recruitment probability bias, this may not have adjusted for the full effect of the bias. There is literature showing that men in committed, romantic relationships have lower testosterone levels than those not in such relationships [245]. It remains unclear whether men have lower testosterone levels because of involvement in a relationship or whether men with lower testosterone levels are more inclined to seek such relationships [246]. Interestingly, a study in Kenyan Swahili men showed that unmarried men had similar testosterone levels to monogamously married men (a result in contrast to North American studies [245, 246]), but polygymously married men (with 2 wives) had significantly higher levels [247]. It is also possible that the effect of marriage or living with a partner may be due to those men being fatter. However, this effect was independent of waist circumference in the models. All studies investigating the effect of marital/relationship status on testosterone levels have used salivary testosterone as opposed to the serum measurements used in the present study. The complex interplay of behaviour, power and role within committed relationships is likely to be involved in the association with lower testosterone levels in men. It has been shown that testosterone is positively related to power motivation in men [248]; in heterosexual partners the male is more likely to exhibit adaptive problem-solving behaviours and social support provision when both the man and the woman have lower

testosterone levels, in contrast, the woman exhibits these adaptive behaviours if she has higher and the male has lower testosterone levels [249].

Age was the common independent predictor of all measured serum testosterone and SHBG concentrations; younger age was related to higher, whilst older age was related to lower testosterone levels with the reverse relationship being true for SHBG. This association has been shown widely in both cross-sectional [54, 57, 58, 59 , 71, 72, 74, 224-226] and longitudinal studies showing that there is an element of direct reduction of testosterone secretion by increased ageing [24, 35, 47, 67, 227].

The hypothesis that increased levels of chronic disease in older age may contribute to the reduction in serum testosterone and increase in SHBG levels has been rejected by some studies [24, 67]. Men with certain chronic diseases (e.g. diabetes) at any age have reduced testosterone and increased SHBG levels, but the rate of age-related change is similar to that of healthy men [24, 67]. In the present study, the presence of metabolic, endocrine and/or nutritional health conditions, including hypercholesterolaemia appeared to relate more to higher SHBG levels than to serum testosterone concentration. It is possible that this effect is through a greater percentage of body fat, although in the present model the effect is independent of waist circumference. The present data are limited by the cross-sectional nature of the analyses which prevents the temporality of the associations from being determined.

Being a current smoker appears to be associated with higher serum total and free, but not bioavailable testosterone levels independent of age and other co-variates. Similar associations between smoking and total and free testosterone have been reported previously in epidemiological, cross-sectional [58, 250, 251] and longitudinal studies [230]. Again, it is possible that lower body fat in smokers moderates this effect but in the present models the effect is independent of waist circumference. In another longitudinal study, a greater number of pack years of cigarette smoking was associated with greater decline in serum total testosterone over 13 years [47]. A case-control study of smokers and non-

smokers, matched for age and body mass index, showed higher total and free testosterone but similar BT in smokers when compared to non-smokers [231]. In contrast to the present study, English et al. (2001) also showed higher SHBG levels in smokers [231]. The mechanisms by which cigarette smoking affects endogenous total and free testosterone have not been proven but may relate to lower levels of body fat in smokers.

Having a lower daily alcohol intake was associated with lower bioavailable but not total or free testosterone, independent of age and other co-variates. The literature is indecisive on the association between alcohol intake and endogenous testosterone levels. Most cross-sectional studies report no associtation between alcohol intake and serum total, bioavailable and free testosterone [58, 168, 250, 252] as does one longitudinal study [47]. A European, cross-sectional study reported that a lower alcohol intake was associated with higher total testosterone and SHBG levels [251]. In alcoholic men, testosterone levels were normal after 7 alcohol-free days, but decreased rapidly and significantly in men subsequently allowed unlimited alcohol compared to those who maintained abstinence[253]. In detoxifying alcoholics, serum total testosterone was low (but within the normal range) 1day after admission to a detoxifying clinic (while sober) and after 5 days, at discharge. These levels were significantly higher after 3 weeks of sobriety [254]. FSH and LH were high initially, but were significantly depressed during detoxification in accordance with the change in total testosterone [254]. One mechanism by which alcohol may affect serum testosterone levels is by toxic effects on the liver. FSH, LH, and testosterone levels all increased significantly following successful liver transplantation in alcoholic but not in non-alcoholic men with severe liver disease [255]. However, in this study, liver transplantation did not fully recover FSH, LH and testosterone levels to those of controls. Some residual alcohol-induced injury to the hypothalamic-pituitary-gonadal axis may persist despite successful liver transplantation [255]. Even in the absence of liver dysfunction, there is still a direct toxic effect of ethanol on testosterone synthesis resulting in acutely decreased values [254]. The long-term effects of

regular and moderate to high alcohol use on serum testosterone levels and the mechanism of these effects remain to be determined.

The majority of other independent predictors of testosterone and SHBG levels in serum are metabolic in origin. Larger waist circumference, impaired glycaemic control and taking medications for general and endocrine, metabolic and nutritional disease all appear to be independently related to lower testosterone levels, no matter which measurement is used. Similar associations with abdominal obesity and aspects of the metabolic syndrome have been reported by both cross-sectional [256-258], case-control [105] and longitudinal studies [259], although some cross-sectional studies, most notably Denti et al. (2000) [57] reported a lack of association. Serum testosterone appears to be reduced and SHBG increased by abdominal or visceral obesity in men and replacement of testosterone in young hypogonadal and older men with low-normal testosterone levels reduces central fat mass [91]. A decline in testosterone in older males leads to an increase in leptin levels [60]. In addition, as reported in other cross-sectional studies [232], the present study shows that having high levels of total serum cholesterol (including a clinical diagnosis) in the presence of lower LDL and HDL cholesterol levels and having other metabolic, endocrine or nutritional conditions, is associated with lower SHBG levels. This presumably relates to reduced rates of production in the liver in a high lipid environment. Abdominal or visceral obesity is a major risk factor for cardiovascular disease and type 2 diabetes mellitus. The co-existence of visceral obesity, increased blood lipid levels, hypertension and impaired glucose tolerance defines the metabolic syndrome, a prime factor behind cardiovascular morbidity and mortality [90]. It is likely that low serum testosterone levels are a marker of this syndrome. The cause and effect relations between aspects of the metabolic syndrome and age-related changes in the hypothalamic-pituitary-testicular axis remain to be fully elucidated.

Of the gonadotropins (the known physiological regulators of gonadal steroid production and secretion), FSH but not LH was inversely related to all measures of serum testosterone and positively to SHBG

prior to adjustment for all co-variates. LH is traditionally known as the major stimulator of testicular Leydig cell production and secretion of testosterone, while FSH is primarily responsible for the stimulation of spermatogenesis by the Sertoli cells; a process that is also dependent on testosterone. It has been shown in rats [260] that spermatogenesis can proceed with testosterone alone, in the absence of gonadotropins. The lack of association between serum testosterone and LH levels in the present study is probably due to the pulsatile nature of LH secretion and its subsequent direct inhibition by testosterone [1]. It is possible that FSH has an inhibitory role in the regulation of testosterone production and secretion by the Leydig cells and/or the availability of testosterone inhibits the pituitary secretion of FSH, thereby explaining the inverse association with all fractions of bound and free testosterone. The association with SHBG is less clear and may be modulated via the testosterone level itself. There was an independent association between total testosterone and SHBG concentrations in serum and these two compounds are likely to be a part of a dual-directional feedback loop regulating the balance between the hormone and the binding protein [261].

In addition to the continuous linear associations, the present study assessed the ability of associated factors to predict low levels of serum total and bioavailable testosterone. Low BT was defined as less than 3.1 nmol/L as indicated in Chapter 3.0. Low total T was defined as less than 8 nmol/L, the current definition of hypogonadism required for testosterone supplementation in Australia. A higher level of less 12 nmol/L was also assessed. Age greater than 60 years was the best single predictor of a low BT and addition of any other factor (including waist circumference greater than 102 cm) did not improve the ability to predict men with low BT. In contrast, a total T less than 8 nmol/L was best predicted by being 60 or older and having serum triglycerides greater than 2 mmol/L. Using HbA1c of 6.2% or greater was also highly predictive of total T less than 8 nmol/L and the addition of any other factors did not enhance the predictive value. For the prediction of men with total T less than 12 nmol/L, being 60 years or older, having a waist circumference greater than 102 cm, an HbA1c of 6.2% or greater and being a non-

smoker were all of similar value. The best predictor of total T < 12 was being a non-smoker with a waist circumference greater than 102 cm ans fasting serum triglycerides greater than 2 mmol/L.

5.2. THE ASSOCIATIONS OF TOTAL, BIOAVAILABLE AND FREE TESTOSTERONE AND SHBG WITH BODY COMPOSITION, MUSCLE STRENGTH AND PHYSICAL FUNCTION.

SUMMARY

Low levels of gonadal steroids and changes in the activity of the IGF axis may be markers of the metabolic syndrome associated with visceral obesity and sarcopenia. This chapter describes the associations of the various measures of serum testosterone and SHBG with lean mass and abdominal fat, handgrip strength and physical function. Data were from the FAMAS as described in Chapter 4.0. Abdominal fat percentage was inversely associated with total testosterone and SHBG levels independent of age and demographic, behavioural risk factor, chronic disease and medication covariates. Whole body lean mass was independently and positively associated with total T and SHBG levels. Neither maximal handgrip strength nor physical function were associated with any of the measures of serum testosterone or SHBG. The most notable associations with body composition, handgrip strength and physical function were with clinical and laboratory indicators of metabolic disease such as blood pressure and fasting serum lipids, glucose and insulin levels. In addition, lower daily dietary intakes of total energy and protein were associated with lower lean body mass and weaker handgrip strength but not with lower abdominal fat. With ageing there is a multi-factorial, physiological anorexia that is associated with sarcopenic weight loss, increased frailty, functional decline and premature morbidity and mortality. These results suggest that serum total testosterone and SHBG, dietary intake, increased chronic disease and medication use with older age are critical factors in the occurrence of age related sarcopenia. Lower serum testosterone and SHBG levels, increased chronic

disease and medication use with older age are involved in higher levels of abdominal fat. Together these factors may contribute to greater functional decline and increased morbidity and mortality.

INTRODUCTION

Muscle mass decreases and fat mass increases with increasing age. In the New Mexico Ageing Process Study the best predictor of loss of muscle mass and strength (sarcopenia) was free testosterone. Other predictors included age, caloric intake, physical activity, and IGF-1 (reflecting low growth hormone levels) [60]. Sarcopenia leads to frailty, an important precursor of subsequent functional deterioration and death. Frailty has been objectively defined by the criteria of weight loss, exhaustion, weakness (grip strength), slow walking speed and low physical activity. A number of hormones are believed to play a role in the pathophysiology of frailty. These include testosterone, insulin growth factor-1 and vitamin D. Cytokine excess (especially tumour necrosis factor α and interleukin-6) also appears to produce frailty. Persons with diabetes mellitus are at high risk of developing premature frailty. Weight loss, which can be due to sarcopenia, anorexia, cachexia or dehydration, is a hallmark of frailty. Obesity, particularly when the fat is distributed within the abdomen (visceral) is associated with low plasma T [18, 87, 88]. Conversely, decreased testosterone levels in men are associated with increased accumulation of visceral fat [90, 262], which is reversible upon testosterone administration [90, 91]. Therefore, low levels of gonadal steroids and changes in the activity of the IGF axis may be markers of the metabolic syndrome associated with visceral obesity, increasing age and associated impaired glucose tolerance and cardiovascular disease, resulting in accelerated frailty and death.

This chapter describes the associations of the various measures of serum testosterone and SHBG with lean and fat body mass, handgrip strength and physical function.

MATERIALS AND METHODS

PARTICIPANT SELECTION

Participants were male volunteers (N = 568), living in the North and West suburbs of Adelaide and recruited at random from the Electronic White Pages as described in Chapter 4.0.

MEASUREMENTS

All assessments were performed according to the methods described in Chapter 4.0. Specifically, morning blood samples were obtained and assayed for total T and SHBG and FT was calculated as described in Chapter 4.0. BT was measured and cBT calculated as described in Chapter 3.0. Lean body mass (%) and abdominal fat (%) mass were measured by DEXA and maximal handgrip strength was measured by dynamometry as described in Chapter 4.0. Physical function, limitations in usual role activities because of physical problems and bodily pain were assessed using thew SF-36 as described in Chapter 4.0. Cigarette smoking, exercise and alcohol intake and the daily dietary intake of energy, fat, carbohydrate and protein were assessed by questionnaire as described in Chapter 4.0. Chronic disease included but was not limited to depression, diabetes, hypertension, hypercholesterolaemia, enlarged prostate and prostate cancer and current medications were determined by self-report. History of surgical procedures including prostatectomy, trans-urethral resection of prostate (TURP) and other urogenital surgery was obtained by questionnaire as described in Chapter 4.0.

STATISTICAL ANALYSIS

Initially, bivariate associations with serum testosterone and SHBG levels were investigated. For categorical data including demographics, chronic disease, urogenital surgery and medication use, mean

serum testosterone and SHBG concentrations were compared using a Wald test of significance. In these cases, data presented are means ± S.E. with associated 95% confidence intervals and comparative F and P statistics. Associations between continuous variables including SBP, waist circumference, cholesterol levels and other risk factor data, were determined by simple linear regression analysis, where data are presented as regression coefficients and associated 95% confidence intervals and R^2 and P statistics.

All associations were then adjusted for age using linear regression with age as a continuous variable.

Multiple linear regression analysis was used to account for confounding variables, considered to be variables that related to both the measure of plasma T of interest and the outcome variable at a level of $P < 0.05$. For multiple linear regression analysis the regression coefficient and 95% confidence intervals (CI's) are reported. All analyses were performed on stratified and probability weighted data as described in Chapter 4.0.

RESULTS

DEMOGRAPHICS

Five hundred and seventeen men (91%) returned for clinic visit 2 for the assessment of body composition by DEXA. Five hundred and forty-three men performed grip strength testing on the dominant and 547 on the non-dominant hand; 535 performed the test bilaterally. There were only subtle differences between dominant and non-dominant maximal grip strength relationships with other variables and the mean difference between the two was 2.91 ± 0.21 Kg (95% CI 2.50 – 3.33 Kg). Thus, for ease of reporting, maximal grip strength data is reported as the mean of maximal strength of both hands combined. Analyses are also performed on maximal grip strength expressed relative to arm lean mass (Kg/g arm lean mass).

Mean whole body lean mass (absoulute, grams), abdominal fat percentage, and maximal grip strength (combined hands) are shown by age, school-leaving age, highest post-secondary qualification, annual gross household income and work status, receipt of a DSS pension, marital status and country of birth in Appendix V (Tables V.I – V.III). Whole body lean mass (%) and handgrip strength (absolute & relative to arm lean mass (Kg/g arm lean mass)) were inversely and abdominal fat mass was positively associated with increasing age (Figure 5.2.1). Mean physical function, limitations in usual role activities because of physical problems (role physical) and bodily pain of the cohort have been previously described by age, school-leaving age, highest post-secondary qualification, annual gross household income and work status, receipt of a DSS pension, marital status and country of birth in Chapter 4.0 (Table 4.18 – 4.20 respectively). Mean physical function, role physical and bodily pain were all inversely associated with increasing age (Figure 5.2.2). Age-adjusted associations of lean body mass, maximal handgrip strength, physical function, role physical and bodily pain with demographics are shown in

Table 5.2.1. In age-adjusted analyses, abdominal fat percentage was not associated with any demographic variables. Greater maximal handgrip strength, physical function, fewer limitations to usual role activities because of physical problems and less bodily pain were all associated with higher gross annual household income. Higher maximal handgrip strength, greater physical function, fewer limitations to usual role activities because of physical problems and less bodily pain were all associated with not receiving a DSS pension and being employed. Additionally, higher maximal handgrip strength, greater physical function and fewer limitations to usual role activities because of physical problems were associated with being married or living with a partner. Expressing grip strength relative to arm lean mass (Kg/g of arm lean mass) resulted in no age-independent associations with demographic variables. Greater physical function was also associated with higher post-school qualifications and men born outside of Australia had higher lean body mass.

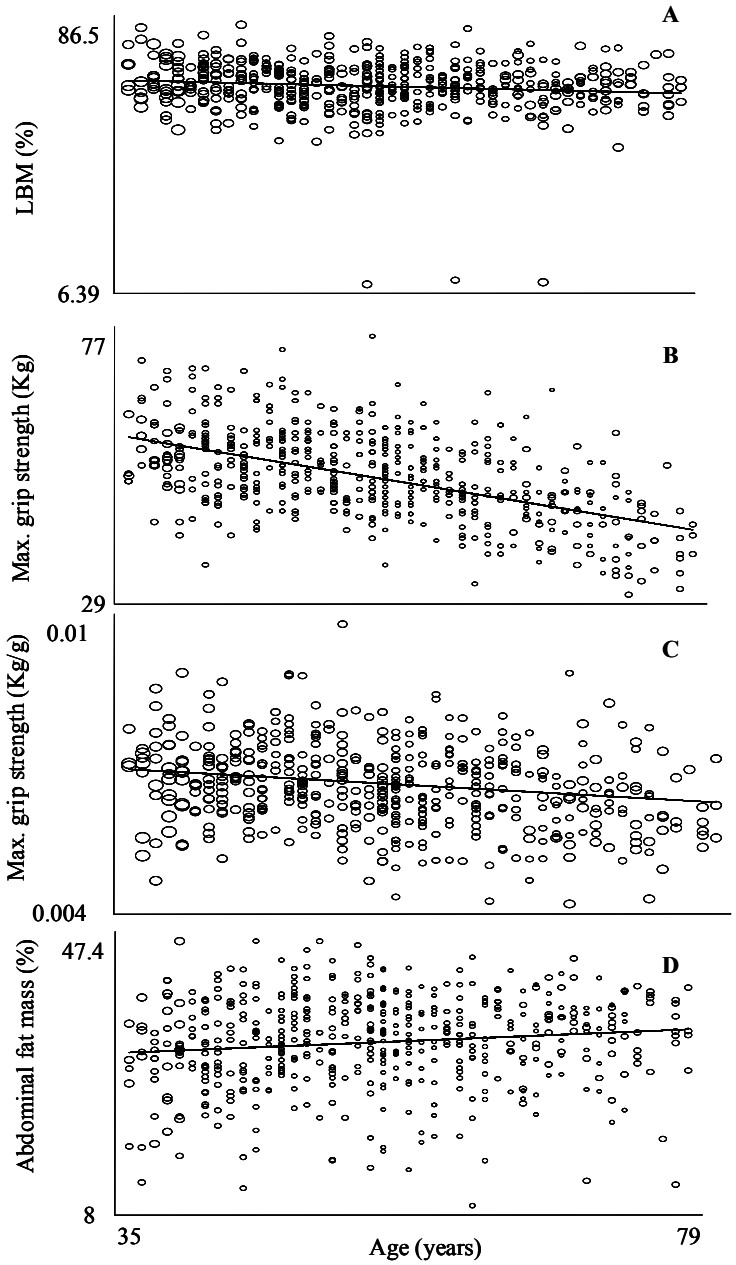

Figure 5.2.1 Associations of lean body mass (panel A), absolute maximal handgrip strength (panel B), relative maximal handgrip strength (panel C) and abdominal fat mass (panel D) with age

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Lean body mass (A) [Coeff. = -0.091 (95% CI -0.151 - -0.03) P = 0.004], Absolute maximal handgrip strength (B) [Coeff. = -0.391 (-0.446 - -0.337) P < 0.0001], Relative maximal handgrip strength (C) [Coeff. = -0.00002 (-0.00003 - -0.00001) P < 0.0001], Abdominal fat mass [Coeff. = 0.079 (0.021 – 0.137) P = 0.008].

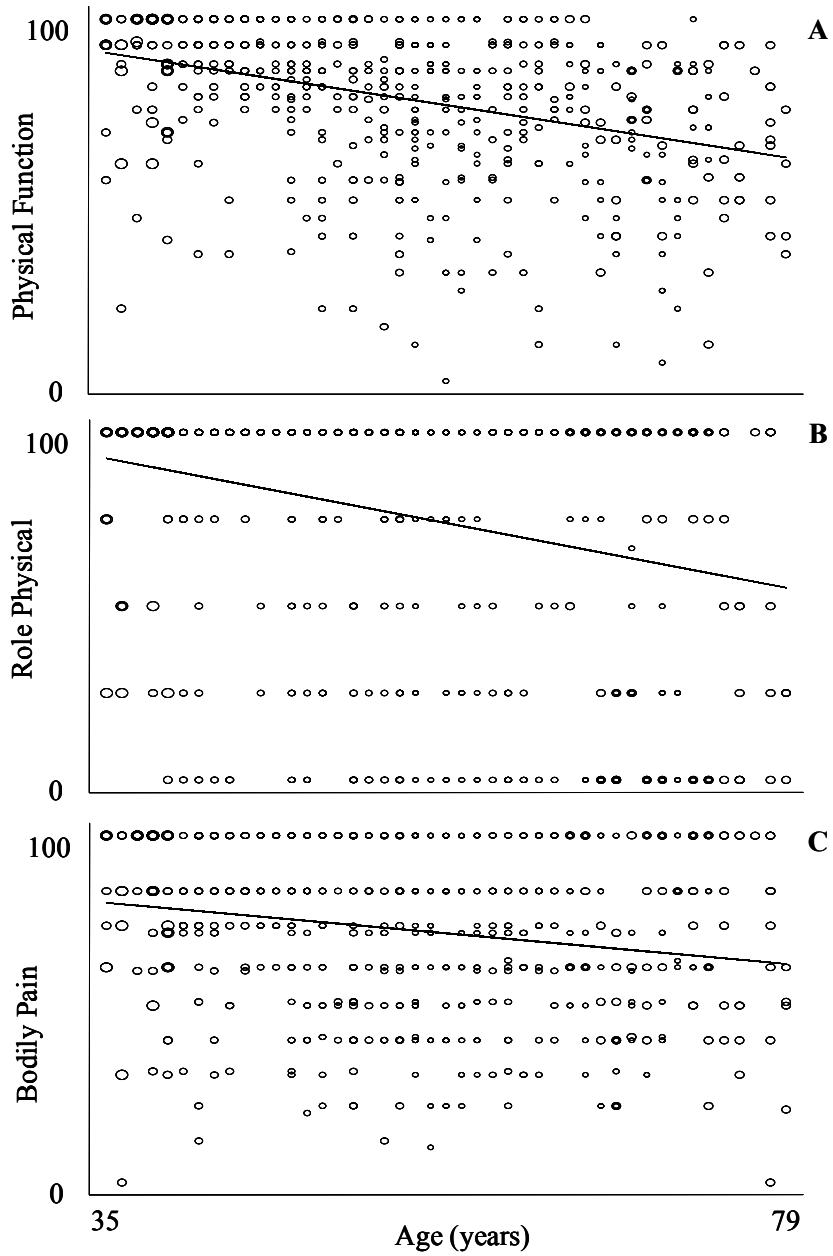

Figure 5.2.2 Associations of Physical function (panel A), Role physical (panel B) and Bodily pain (panel C), as measured by the SF-36, and age

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Physical function (A) [Coeff. = -0.656 (95% CI -0.797 - -0.515) P < 0.0001], Role physical (B) [Coeff. = -0.846 (-1.126 - -0.567) P < 0.0001], Bodily pain (C) [Coeff. = -0.401 (-0.589 – -0.213) P < 0.0001].

	Lean body mass	
	Coeff (95% CI)	P
Birth country	1.31 (0.343 – 2.281)	0.008
	Maximal handgrip strength	
Gross annual household income	0.98 (0.51 - 1.45)	< 0.0001
Work status	-1.02 (-1.87 - -0.17)	0.019
DSS pension	2.78 (1.33 - 2.44)	< 0.0001
Marital status	-0.81 (-1.60 - -0.02)	0.044
	Physical function	
Gross annual household income	3.27 (2.03 - 4.51)	< 0.0001
Work status	-9.53 (-12.79 - -6.27)	< 0.0001
DSS pension	13.55 (8.63 - 18.47)	< 0.0001
Marital status	-2.63 (-4.80 - -0.46)	0.018
Post school qualifications	2.53 (0.13 - 4.93)	0.039
	Role physical	
Gross annual household income	4.98 (2.53 - 7.43)	< 0.0001
Work status	-17.54 (-23.26 - -11.32)	< 0.0001
DSS pension	23.38 (14.99 - 31.78)	< 0.0001
Marital status	-7.02 (-11.22 - -2.81)	0.001
	Bodily pain	
Gross annual household income	2.89 (1.29 - 4.50)	< 0.0001
Work status	-8.73 (-12.26 - -5.20)	< 0.0001
DSS pension	9.80 (4.03 - 15.57)	0.001

Table 5.2.1 Significant age-adjusted associations of lean body mass, maximal handgrip strength, physical function, role physical and bodily pain with demographic variables

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

CHRONIC DISEASE RISK FACTORS AND BEHAVIOURS

The non-age-adjusted effect of chronic disease risk factors and behaviours on whole body lean mass (absolute, grams), abdominal fat percentage, maximal grip strength, physical function, role physical and bodily pain are shown in Appendix V (Tables V.IV – V.XV).

The age-adjusted associations of abdominal fat percentage, lean body mass (%), maximal handgrip strength, physical function, role physical and bodily pain with chronic disease risk factors and behaviours are shown in Table 5.2.2. In age-adjusted analyses, whole body lean mass was significantly and inversely associated with systolic and diastolic blood pressure, fasting serum triglycerides, glucose, HbA1c, insulin and dietary fat intake and positively associated with HDL cholesterol. Abdominal fat percentage was significantly and positively associated with SBP, DBP, fasting serum triglycerides, total and LDL cholesterol, fasting serum glucose, HbA1c, insulin and dietary fat intake and inversely associated with serum HDL cholesterol. Maximal handgrip strength was significantly and positively associated with waist circumference, dietary energy, fat, carbohydrate and protein intake. Expressing grip strength relative to arm lean mass (Kg/g of arm lean mass) resulted in different age-independent associations: lower maximal grip strength was associated with higher diastolic blood pressure, larger waist circumference, higher fasting serum triglycerides, glucose and insulin, higher HbA1c, lower total and HDL cholesterol and higher dietary protein intake (data not shown). Physical function was significantly and inversely associated with waist circumference, fasting serum glucose, insulin and HbA1c and positively associated with LDL and HDL cholesterol, physical activity level and non-smoking. Greater limitation in usual role activities because of physical problems was significantly associated with greater waist circumference, HbA1c and fasting serum insulin levels and with lower total and HDL cholesterol levels and current smoking. Greater bodily pain was significantly associated with greater waist circumference and serum triglycerides and lower HDL cholesterol levels.

	Abdominal % fat			Physical function	
	Coeff (95% CI)	P		Coeff (95% CI)	P
SBP	0.14 (0.10 - 0.18)	< 0.0001	Waist circumference	-0.32 (-0.47 - -0.17)	< 0.0001
DBP	0.21 (0.13 - 0.28)	< 0.0001	LDL cholesterol	1.96 (0.07 - 3.85)	0.042
Serum triglycerides	1.04 (0.48 - 1.60)	0.0001	HDL cholesterol	7.07 (1.30 - 12.85)	0.016
Serum total cholesterol	1.10 (0.49 - 1.71)	0.0002	Fasting glucose	-1.59 (-3.10 - -0.08)	0.04
LDL cholesterol	1.15 (0.45 - 1.86)	0.001	HbA1c	-3.09 (-5.22 - -0.96)	0.005
HDL cholesterol	-5.53 (-7.61 - -3.46)	< 0.0001	Fasting insulin	-0.27 (-0.43 - -0.12)	0.001
Fasting glucose	0.91 (0.41 - 1.41)	< 0.0001	Physical activity level	3.34 (1.64 - 5.05)	< 0.0001
HbA1c	1.32 (0.54 - 2.10)	0.001	Smoking	4.70 (0.88 - 8.53)	0.016
Fasting insulin	0.29 (0.16 - 0.43)	< 0.0001			
Dietary fat intake	0.02 (0.003 - 0.04)	0.024			
	Lean body mass			Role physical	
SBP	-0.127 (-0.184 - -0.07)	< 0.0001	Waist circumference	-0.41 (-0.67 - -0.14)	0.003
DBP	-0.175 (-0.247 - -0.104)	< 0.0001	Serum total cholesterol	3.22 (0.20 - 6.23)	0.037
Serum triglycerides	-0.654 (-1.129 - -0.179)	0.007	HDL cholesterol	20.66 (9.27 - 32.05)	< 0.0001
HDL cholesterol	4.71 (2.48 – 6.94)	< 0.0001	HbA1c	-4.79 (-8.71 - -0.86)	0.017
Fasting glucose	-0.905 (-1.44 - -0.366)	0.001	Fasting insulin	-0.52 (-0.85 - -0.20)	0.002
HbA1c	-1.24 (-2.02 - -0.469)	0.002	Smoking	8.54 (1.18 - 15.90)	0.023
Fasting insulin	-0.263 (-0.395 - -0.13)	< 0.0001			
Dietary fat intake	-0.03 (-0.052 - -0.008)	0.007			

	Maximal handgrip strength			Bodily pain	
Waist circumference	0.06 (0.01 - 0.11)	0.013	Waist circumference	-0.25 (-0.43 - -0.07)	0.006
Dietary energy intake	0.0003 (0.0001 - 0.0005)	0.002	Serum triglycerides	-2.23 (-3.82 - -0.65)	0.006
Dietary fat intake	0.02 (0.002 - 0.037)	0.032	HDL cholesterol	9.48 (2.50 - 16.46)	0.008
Dietary carbohydrate intake	0.012 (0.005 - 0.019)	0.001			
Dietary protein intake	0.026 (0.01 - 0.04)	0.002			

Table 5.2.2 Significant age-adjusted associations of abdominal fat percentage, lean body mass, maximal handgrip strength, physical function, role physical and bodily pain with chronic disease risk factors and behaviours

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

CHRONIC DISEASE, SURGICAL PROCEDURES AND MEDICATIONS

The non-age-adjusted effect of chronic disease, surgical procedures and medication use on whole body lean mass (absolute, grams), abdominal fat percentage, maximal grip strength, physical function, limitations to usual role activities as a result of physical problems and bodily pain are shown in Appendix V (Tables V.XVI – V.XXI).

Age-adjusted associations of abdominal fat percentage, lean body mass (%), maximal handgrip strength, physical function, role physical and bodily pain with chronic disease, surgical procedures and medication use are shown in Table 5.2.3. In age-adjusted analyses, greater whole body lean mass was significantly associated with having had a TURP and not having a metabolic, endocrine or nutritional health condition. A greater abdominal fat percentage was significantly associated with hypercholesterolaemia, hypertension and prostate removal. A lower percentage of abdominal fat was associated with past TURP and current respiratory and metabolic, endocrine or nutritional health conditions. Lower maximal handgrip strength was significantly associated with thyroid disorders, prostate cancer and taking medications for general and urinary health conditions. Expressing grip strength relative to arm lean mass (Kg/g of arm lean mass) resulted in different age-independent associations: lower max grip strength was associated with diabetes, hypertension, prostatectomy, musculoskeletal health condition and taking neurological medication (data not shown). Better physical function, fewer limitations to usual role activities because of physical problems and less bodily pain were significantly associated with many health conditions and medications and with bladder surgery (Table 5.2.3).

	Abdominal % fat	
	Coeff (95% CI)	P
Hypercholesterolaemia	1.42 (0.18 - 2.66)	0.024
Hypertension	2.08 (0.73 - 3.43)	0.003
Probability of OSA	12.46 (9.54 - 15.38)	< 0.0001
Prostate removal	3.82 (1.32 - 6.31)	0.003
TURP	-2.96 (-5.42 - -0.49)	0.019
Health condition, respiratory	-4.36 (-8.11 - -0.61)	0.023
Health condition; Met. Endo. Nut.	2.70 (0.49 - 4.90)	0.017
	Lean body mass	
TURP	4.61 (2.12 – 7.09)	< 0.0001
Health condition; Met. Endo. Nut.	-3.00 (-5.65 - -0.346)	0.027
	Maximal handgrip strength	

	Role physical	
	Coeff (95% CI)	P
Angina	-30.79 (-46.49 - -15.08)	< 0.0001
Anxiety	-20.21 (-32.14 - -8.29)	0.001
Depression	-24.06 (-34.63 - -13.49)	< 0.0001
Hypercholesterolaemia	-13.31 (-20.51 - -6.12)	< 0.0001
Hypertension	-7.90 (-15.07 - -0.73)	0.031
Insomnia	-31.96 (-42.43 - -21.50)	< 0.0001
Osteoarthritis	-23.44 (-36.67 - -10.20)	0.001
Rheumatoid arthritis	-18.25 (-35.17 - -1.34)	0.035
Probability of OSA	-29.94 (-43.78 - -16.11)	< 0.0001
Bladder surgery	-27.88 (-46.54 - -9.23)	0.003
Health condition, musculoskeletal	-18.00 (-28.17 - -7.83)	0.001
Health condition, psychological	-22.81 (-44.74 - -0.88)	0.041
Medication, general health	-13.92 (-23.40 - -4.45)	0.004
Medication, digestive	-15.11 (-24.94 - -5.28)	0.003
Medication, circulatory	-11.64 (-20.04 - -3.23)	0.007
Medication, musculoskeletal	-15.19 (-24.81 - -5.58)	0.002

Thyroid disorder	-4.88 (-7.51 - -2.26)	< 0.0001	Medication, psychological	-27.50 (-39.41 - -15.59)	< 0.0001
Prostate Cancer	-5.22 (-7.92 - -2.52)	< 0.0001	Medication; Met. Endo. Nut.	-15.06 (-23.83 - -6.28)	0.001
Medication, general health	-1.75 (-3.50 - -0.01)	0.049	Medication, urological	-49.30 (-71.27 - -27.33)	< 0.0001
Medication, urological	-9.96 (-14.22 - -5.70)	< 0.0001		Bodily pain	
	Physical function		Angina	-15.32 (-23.95 - -6.69)	0.001
Angina	-16.54 (-24.40 - -8.67)	< 0.0001	Anxiety	-15.98 (-23.15 - -8.81)	< 0.0001
Anxiety	-7.39 (-13.58 - -1.21)	0.019	Asthma	-7.00 (-13.98 - -0.03)	0.049
Asthma	-5.94 (-11.81 - -0.07)	0.047	Depression	-16.87 (-22.70 - -11.04)	< 0.0001
Depression	-10.44 (-15.62 - -5.27)	< 0.0001	Diabetes	-7.33 (-14.30 - -0.36)	0.039
Diabetes	-6.21 (-12.17 - -0.24)	0.041	Hypercholesterolaemia	-7.54 (-12.12 - -2.96)	0.001
Hypercholesterolaemia	-5.21 (-8.81 - -1.43)	0.007	Insomnia	-18.09 (-24.53 - -11.65)	< 0.0001
Hypertension	-5.78 (-9.63 - -1.93)	0.003	Osteoarthritis	-21.57 (-27.92 - -15.22)	< 0.0001
Insomnia	-10.67 (-16.94 - -4.40)	0.001	Rheumatoid arthritis	-13.64 (-23.34 - -3.94)	0.006
Osteoarthritis	-13.48 (-20.69 - -6.27)	< 0.0001	Probability of OSA	-18.96 (-28.43 - -9.48)	< 0.0001
Rheumatoid arthritis	-8.40 (-15.23 - -1.57)	0.016	Bladder surgery	-20.70 (-32.81 - -8.59)	0.001
Probability of OSA	-18.85 (-26.17 - -11.00)	< 0.0001	Health condition, musculoskeletal	-14.85 (-20.94 - -8.75)	< 0.0001
Bladder surgery	-17.51 (-32.09 - -2.93)	0.019	Health condition, neurological	-16.68 (-32.41 - -0.95)	0.038
Health condition, musculoskeletal	-9.70 (-14.70 - -4.70)	< 0.0001	Medication, general health	-10.86 (-16.68 - -5.03)	< 0.0001

Health condition, neurological	-13.98 (-27.21 - -0.74)	0.039	Medication, digestive	-7.50 (-13.35 - -1.66)	0.012
Medication, general health	-6.20 (-11.01 - -1.39)	0.012	Medication, musculoskeletal	-19.61 (-25.24 - -13.98)	< 0.0001
Medication, digestive	-7.30 (-12.34 - -2.26)	0.005	Medication, neurological	-10.30 (-19.52 - -1.09)	0.028
Medication, circulatory	-6.78 (-11.22 - -2.34)	0.003	Medication, psychological	-16.53 (-23.56 - -9.50)	< 0.0001
Medication, musculoskeletal	-11.47 (-16.85 - -6.10)	< 0.0001	Medication; Met. Endo. Nut.	-7.25 (-12.51 - -1.99)	0.007
Medication, psychological	-11.34 (-17.93 - -4.75)	0.001	Medication, urological	-22.26 (-37.57 - -6.94)	0.004
Medication; Met. Endo. Nut.	-6.17 (-10.88 - -1.47)	0.01			

Table 5.2.3 Significant age-adjusted associations of abdominal fat percentage, lean body mass, maximal handgrip strength, physical function, role physical and bodily pain with chronic disease, urogenital surgical history and medication use

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

SERUM TESTOSTERONE

Whole body lean mass

In age-adjusted analyses, total T and SHBG were positively associated with whole body lean mass (%) (Table 5.2.4). Bioavailable testosterone, measured and calculated, was not associated with lean body mass independent of age.

Abdominal fat percentage

In age-adjusted analyses, total T, FT and SHBG were inversely associated with abdominal fat mass percentage (Table 5.2.4) but there was no association with either measured or calculated BT.

Maximal handgrip strength

In age-adjusted analyses, no measures of serum testosterone or SHBG were associated with maximal handgrip strength. Expressing grip strength relative to arm lean mass (Kg/g of arm lean mass) resulted in age-independent positive associations with both total and free T (Coeff. = 0.00004 (95% CI 9.0 – 0.0), P = 0.013 & Coeff. = 1.00 (95% CI 7.0 – 0.0), P = 0.001, respectively).

Physical function, role limitations and bodily pain

In age-adjusted analyses, serum free testosterone (Table 5.2.4), but no other measures of testosterone or SHBG, was positively associated with physical function. No measures of serum testosterone or SHBG were associated with physical role limitations or bodily pain.

	Lean body mass	
	Coeff (95% CI)	P
Total T	0.357 (0.208 – 0.507)	< 0.0001
SHBG	0.114 (0.051 – 0.178)	0.0001
	Abdominal fat mass (%)	
Total T	-0.40 (-0.55 - -0.26)	< 0.0001
FT	-0.01 (-0.02 - -0.0006)	0.039
SHBG	-0.14 (-0.20 - -0.08)	< 0.0001
	Physical function	
FT	0.01 (0.001 - 0.029)	0.033

Table 5.2.4 Significant age-adjusted associations of lean body mass, abdominal fat percentage and physical function with chronic serum testosterone and SHBG measurements

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

MULTIVARIATE PREDICTIVE MODELS

Whole body lean mass

All testosterone and SHBG models significantly predicted 4% - 19% of the heterogeneity in lean body mass within the cohort (Table 5.2.5). Serum total T and SHBG were independently and positively associated with lean body mass. BT, cBT and FT were not independently associated with lean body mass. The other major independent predictors of lower lean body mass in the total T model was higher systolic blood pressure, higher fasting serum insulin and lower HDL. Older age, higher fasting serum insulin and higher diastolic blood pressure were independent predictors of lower lean body mass in the SHBG model.

Abdominal fat percentage

Total and free testosterone and SHBG models significantly predicted 34%, 21% & 30%, respectively, of the heterogeneity in lean body mass within the cohort (Table 5.2.6). Measured and calculated BT models significantly explained only 5% of the heterogeneity. Serum total testosterone and SHBG, but not BT, cBT or FT, were independently and inversely associated with percentage of abdominal fat (Table 5.2.6). The other major independent predictors of a higher percentage of abdominal fat in these models were higher systolic and diastolic blood pressures, higher fasting serum triglycerides, total cholesterol and insulin levels and lower HDL cholesterol.

	Total T	
	Coeff (95% CI)	P
Serum total T	0.238 (0.101 – 0.375)	0.001
Age	-0.01 (-0.098 – 0.077)	0.818
Systolic blood pressure	-0.093 (-0.167 - -0.019)	0.013
Diastolic blood pressure	-0.022 (-0.108 – 0.064)	0.615
Fasting serum trigycerides	0.305 (-0.141 – 0.751)	0.180
Fasting HDL cholesterol	2.44 (0.047 – 4.82)	0.046
Fasting serum glucose	-0.322 (-1.03 – 0.388)	0.373
HbA1c	0.25 (-0.757 – 1.257)	0.626
Fasting serum insulin	-0.183 (-0.297 - -0.068)	0.002
Daily fat intake	-0.016 (-0.036 – 0.004)	0.126
Health condition; Met. Endo. Nut.	-0.804 (-2.59 – 0.985)	0.377
	BT	
Serum BT	0.292 (-0.324 – 0.908)	0.352
Age	-0.039 (-0.121 – 0.043)	0.350
Fasting serum glucose	-0.546 (-1.33 – 0.234)	0.170
HbA1c	-0.584 (-1.69 – 0.52)	0.299
	cBT	
cBT	0.131 (-0.359 – 0.621)	0.599
Age	-0.054 (-0.128 – 0.02)	0.149
Fasting serum glucose	-0.577 (-1.36 – 0.209)	0.150
HbA1c	-0.608 (-1.71 – 0.494)	0.279
	FT	
FT	0.007 (-0.002 – 0.016)	0.132
Age	-0.063 (-0.135 – 0.009)	0.084
Fasting serum trigycerides	-0.239 (-0.692 – 0.213)	0.299
Fasting serum glucose	-0.206 (-1.00 – 0.587)	0.609

HbA1c	0.131 (-1.05 – 1.31)	0.828
Fasting serum insulin	-0.229 (-0.361 - -0.096)	0.001
Daily fat intake	-0.017 (-0.038 – 0.005)	0.122
	SHBG	
SHBG	0.074 (0.018 – 0.13)	0.01
Age	-0.106 (-0.174 - -0.037)	0.003
Diastolic blood pressure	-0.129 (-0.20 - -0.058)	< 0.0001
Fasting serum trigycerides	0.258 (-0.166 – 0.681)	0.233
Fasting HDL cholesterol	2.36 (-0.034 – 4.75)	0.053
Fasting serum glucose	-0.302 (-0.781 – 0.177)	0.217
Fasting serum insulin	-0.12 (-0.324 - -0.075)	0.002
Health condition; Met. Endo. Nut.	-0.57 (-2.81 – 1.67)	0.617

Table 5.2.5 Predictive models of serum testosterone and SHBG for lean body mass

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(11, 502) = 13.94$, $P < 0.0001$, $R^2 = 0.19$. BT model: $F(4, 510) = 5.10$, $P = 0.0005$, $R^2 = 0.04$. cBT model: $F(4, 510) = 4.97$, $P = 0.0006$, $R^2 = 0.04$. FT model: $F(7, 506) = 5.87$, $P < 0.0001$, $R^2 = 0.13$. SHBG model: $F(8, 505) = 13.36$, $P < 0.0001$, $R^2 = 0.16$.

	Total T	
	Coeff (95% CI)	P
Serum total T	-0.238 (-0.359 - -0.117)	< 0.0001
Age	0.017 (-0.044 - 0.078)	0.581
Systolic blood pressure	0.088 (0.039 - 0.137)	< 0.0001
Diastolic blood pressure	0.022 (-0.062 - 0.107)	0.609
Fasting serum trigycerides	-0.419 (-0.925 - 0.087)	0.105
Fasting serum total cholesterol	1.313 (0.719 - 1.907)	< 0.0001
Fasting HDL cholesterol	-3.79 (-5.96 - -1.62)	0.001
Fasting serum glucose	0.073 (-0.507 - 0.653)	0.804
HbA1c	-0.05 (-0.981 - 0.881)	0.916
Fasting serum insulin	0.227 (0.105 - 0.348)	< 0.0001
Daily fat intake	0.004 (-0.012 - 0.019)	0.661
Hypercholesterolaemia	0.237 (-0.96 - 1.434)	0.697
Hypertension	0.418 (-0.892 - 1.729)	0.531
Health condition; Met. Endo. Nut.	0.272 (-2.58 - 3.12)	0.852
Health condition, respiratory	-1.63 (-4.27 - 1.01)	0.225
	BT	
Serum BT	-0.287 (-0.836 - 0.262)	0.305
Age	0.028 (-0.051 - 0.106)	0.49
Fasting serum glucose	0.489 (-0.281 - 1.258)	0.213
HbA1c	0.715 (-0.463 - 1.89)	0.234
	cBT	
cBT	-0.142 (-0.583 - 0.30)	0.529
Age	0.042 (-0.03 - 0.113)	0.253
Fasting serum glucose	0.517 (-0.258 - 1.29)	0.19
HbA1c	0.737 (-0.438 - 1.91)	0.218
	FT	

FT	-0.008 (-0.016 - 0.0005)	0.067
Age	0.044 (-0.023 - 0.11)	0.198
Fasting serum trigycerides	0.635 (0.126 - 1.145)	0.015
Fasting serum glucose	0.027 (-0.727 - 0.781)	0.944
HbA1c	-0.068 (-1.278 - 1.143)	0.913
Fasting serum insulin	0.261 (0.126 - 0.397)	< 0.0001
Daily fat intake	0.006 (-0.011 - 0.023)	0.51
	SHBG	
SHBG	-0.08 (-0.125 - -0.035)	0.001
Age	0.125 (0.072 - 0.179)	< 0.0001
Diastolic blood pressure	0.133 (0.062 - 0.203)	< 0.0001
Fasting serum trigycerides	-0.441 (-0.924 - 0.042)	0.074
Fasting serum total cholesterol	1.381 (0.795 - 1.966)	< 0.0001
Fasting HDL cholesterol	-3.853 (-6.043 - -1.663)	0.001
Fasting serum glucose	0.176 (-0.216 - 0.568)	0.379
Fasting serum insulin	0.241 (0.113 - 0.369)	< 0.0001
Hypercholesterolaemia	0.243 (-0.904 - 1.39)	0.678
Health condition; Met. Endo. Nut.	0.274 (-2.747 - 3.295)	0.859

Table 5.2.6 Predictive models of serum testosterone and SHBG for abdominal fat mass percentage

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(15, 498) = 10.66$, $P < 0.0001$, $R^2 = 0.34$. BT model: $F(4, 510) = 6.01$, $P = 0.0001$, $R^2 = 0.05$. cBT model: $F(46, 510) = 5.86$, $P = 0.0001$, $R^2 = 0.05$. FT model: $F(7, 506) = 7.34$, $P < 0.0001$, $R^2 = 0.21$. SHBG model: $F(10, 503) = 12.24$, $P < 0.0001$, $R^2 = 0.30$.

Maximal handgrip strength

All testosterone and SHBG models significantly predicted 34% - 37% of the heterogeneity in maximal handgrip strength within the cohort (Table 5.2.7). However, no measure of serum testosterone or SHBG was independently associated with maximal handgrip strength. The major independent predictors of lower maximal handgrip strength in these models were older age, being widowed or never married, having a lower income, waist circumference and daily total energy intake, having prostate cancer and taking urological medications.

Expressing grip strength relative to arm lean mass (Kg/g of arm lean mass) did not result in independent associations with any serum measures of testosterone or SHBG.

Physical function

All testosterone and SHBG models significantly predicted 22% - 30% of the heterogeneity in physical function scores within the cohort (Table 5.2.8). However, no measure of serum testosterone or SHBG was independently associated with physical function. The major independent predictors of lower physical function in these models were older age, being widowed or never married, receiving a DSS pension, having a lower income, larger waist circumference, cigarette smoking, angina and taking general health medications.

Limitation in usual role activities because of physical problems (Role physical)

All testosterone and SHBG models significantly predicted 14% - 23% of the heterogeneity in role physical scores within the cohort (Table 5.2.9). However, no measure of serum testosterone or SHBG was independently associated with role physical. The major independent predictors of greater limitations because of physical problems in these models were older age, being widowed or never married, receiving a DSS pension, having a larger waist circumference and lower fasting serum HDL cholesterol, cigarette smoking, angina, hypercholesterolaemia and taking general health and urological medications.

Bodily pain

All testosterone and SHBG models significantly predicted 7% - 13% of the heterogeneity in bodily pain scores within the cohort (Table 5.2.10). However, no measure of serum testosterone or SHBG was independently associated with bodily pain. The major independent predictors of greater bodily pain in these models were older age, lower income, having a larger waist circumference and higher fasting serum triglycerides, angina, hypercholesterolaemia and taking general health medications.

	Total T	
	Coeff (95% CI)	P
Serum total T	0.094 (-0.006 - 0.195)	0.066
Age	-0.317 (-0.382 - -0.251)	< 0.0001
Gross annual household income	0.707 (0.133 - 1.28)	0.016
Marital status	-0.332 (-1.116 - 0.451)	0.405
DSS pension	1.417 (-0.254 - 3.088)	0.096
Waist circumference	0.07 (0.017 - 0.123)	0.009
Daily energy intake	0.0007 (0.00004 - 0.001)	0.036
Daily fat intake	-0.043 (-0.087 - 0.0008)	0.054
Daily protein intake	0.009 (-0.024 - 0.042)	0.585
	BT	
Serum BT	0.161 (-0.072 - 0.394)	0.176
Age	-0.394 (-0.452 - -0.337)	< 0.0001
Marital status	-0.872 (-1.629 - -0.115)	0.024
Waist circumference	0.062 (0.011 - 0.113)	0.017
Medication, general health	-1.14 (-2.88 - 0.595)	0.197
Medication, urological	-9.48 (-14.31 - -4.65)	< 0.0001
	cBT	
cBT	0.136 (-0.10 -0.373)	0.26
Age	-0.357 (-0.418 - -0.30)	< 0.0001
Waist circumference	0.063 (0.011 - 0.114)	0.018
Daily energy intake	-0.00005 (-0.0005 - 0.0004)	0.845
Daily carbohydrate intake	0.013 (-0.004 - 0.03)	0.131
Prostate cancer	-4.718 (-7.40 - -2.036)	0.001
Medication, general health	-1.652 (-3.404 - 0.099)	0.064
	FT	
FT	0.004 (-0.0006 - 0.009)	0.083

Age	-0.376 (-0.436 - -0.315)	< 0.0001
Marital status	-0.682 (-1.422 - 0.058)	0.071
Waist circumference	0.073 (0.02 - 0.125)	0.007
Daily energy intake	0.005 (-0.025 - 0.035)	0.75
Daily fat intake	-0.204 (-1.316 - 0.909)	0.719
Daily carbohydrate intake	-0.07 (-0.572 -0.431)	0.783
Daily protein intake	-0.062 (-0.575 - 0.451)	0.812
	SHBG	
SHBG	-0.007 (-0.052 - 0.039)	0.775
Age	-0.35 (-0.41 - -0.29)	< 0.0001
Gross annual household income	0.941 (0.473 - 1.409)	< 0.0001
Waist circumference	0.055 (0.003 - 0.107)	0.037

Table 5.2.7 Predictive models of serum testosterone and SHBG for maximal handgrip strength

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(9, 521) = 32.36$, $P < 0.0001$, $R^2 = 0.37$. BT model: $F(6, 528) = 43.40$, $P < 0.0001$, $R^2 = 0.35$. cBT model: $F(7, 527) = 45.46$, $P < 0.0001$, $R^2 = 0.35$. FT model: $F(8, 526) = 30.86$, $P < 0.0001$, $R^2 = 0.35$. SHBG model: $F(4, 526) = 58.40$, $P < 0.0001$, $R^2 = 0.34$.

	Total T	
	Coeff (95% CI)	P
Serum total T	0.22 (-0.081 - 0.521)	0.152
Age	-0.236 (-0.428 - -0.044)	0.016
Gross annual household income	1.28 (-0.093 - 2.66)	0.068
DSS pension	11.67 (5.94 - 17.40)	< 0.0001
Marital status	-1.46 (-3.62 - 0.702)	0.185
Waist circumference	-0.297 (-0.461 - -0.134)	< 0.0001
Fasting HDL cholesterol	0.432 (-4.68 - 5.55)	0.868
Fasting serum glucose	0.815 (-1.06 - 2.69)	0.394
HbA1c	-1.37 (-4.50 - 1.76)	0.389
Fasting serum insulin	0.017 (-0.164 - 0.198)	0.853
Cigarette smoking	3.16 (-0.354 - 6.68)	0.078
Diabetes	-1.84 (-8.50 - 4.83)	0.589
Hypercholesterolaemia	-3.51 (-7.06 - 0.05)	0.054
Hypertension	-3.29 (-7.30 - 0.714)	0.107
	BT	
Serum BT	0.537 (-0.098 - 1.17)	0.097
Age	-0.556 (-0.721 - -0.397)	< 0.0001
Marital status	-2.26 (-4.45 - -0.063	0.044
Waist circumference	-0.29 (-0.45 - -0.131)	< 0.0001
Fasting serum glucose	0.493 (-1.47 - 2.46)	0.622
HbA1c	-1.61 (-4.86 - 1.65)	0.332
Cigarette smoking	4.88 (1.06 - 8.71)	0.012
Diabetes	-2.34 (-9.32 - 4.63)	0.51

	cBT	
cBT	0.339 (-0.262 - 0.939)	0.269
Age	-0.556 (-0.715 - -0.397)	< 0.0001
Waist circumference	-0.294 (-0.451 - -0.137)	< 0.0001
Fasting serum glucose	0.391 (-1.61 - 2.39)	0.701
HbA1c	-1.65 (-5.00 - 1.69)	0.332
Cigarette smoking	5.17 (1.27 - 9.07)	0.009
Diabetes	-2.75 (-9.83 - 4.34)	0.447
Medication, general health	-6.79 (-11.30 - -2.29)	0.003
	FT	
FT	0.011 (-0.002 - 0.024)	0.098
Age	-0.592 (-0.755 - -0.429)	< 0.0001
Marital status	-2.47 (-4.67 - -0.278)	0.027
Waist circumference	-0.26 (-0.43 - -0.09)	0.003
Fasting serum glucose	0.38 (-1.65 - 2.41)	0.713
HbA1c	-1.26 (-4.51 - 1.99)	0.447
Fasting serum insulin	-0.037 (-0.207 - 0.132)	0.666
Cigarette smoking	4.72 (0.932 - 8.50)	0.015
Diabetes	-2.25 (-9.42 - 4.92)	0.538
	SHBG	
SHBG	-0.083 (-0.242 - 0.076)	0.307
Age	-0.326 (-0.51 - 0.142)	0.001
Gross annual household income	3.32 (2.12 - 4.53)	< 0.0001
Waist circumference	-0.36 (-0.517 - -0.203)	< 0.0001
Fasting HDL cholesterol	1.53 (-3.84 - 6.90)	0.577
Fasting serum glucose	-0.028 (-1.42 - 1.36)	0.969

Fasting serum insulin	0.023 (-0.134 - 0.181)	0.77
Angina	-14.31 (-22.14 - -6.48)	< 0.0001
Hypercholesterolaemia	-2.73 (-6.65 - 1.19)	0.172
Medication; Met. Endo. Nut.	-0.282 (-5.07 - 4.46)	0.907

Table 5.2.8 Predictive models of serum testosterone and SHBG for physical function

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(14, 545) = 14.41$, $P < 0.0001$, $R^2 = 0.30$. BT model: $F(9, 556) = 14.73$, $P < 0.0001$, $R^2 = 0.23$. cBT model: $F(8, 557) = 15.20$, $P < 0.0001$, $R^2 = 0.23$. FT model: $F(9, 556) = 15.08$, $P < 0.0001$, $R^2 = 0.22$. SHBG model: $F(10, 549) = 18.24$, $P < 0.0001$, $R^2 = 0.28$.

	Total T	
	Coeff (95% CI)	P
Serum total T	0.305 (-0.22 - 0.83)	0.254
Age	-0.25 (-0.553 - 0.053)	0.106
Gross annual household income	0.498 (-1.89 - 2.88)	0.682
DSS pension	20.50 (11.41 - 29.59)	< 0.0001
Marital status	-5.75 (-9.81 - -1.69)	0.006
Waist circumference	-0.244 (-0.523 - 0.036)	0.087
Fasting serum total cholesterol	2.59 (-0.107 - 5.30)	0.06
Fasting HDL cholesterol	12.10 (1.47 - 22.74)	0.026
HbA1c	-0.608 (-3.92 - 0.271)	0.719
Fasting serum insulin	-0.077 (-0.488 - 0.333)	0.711
Cigarette smoking	6.27 (-0.302 - 12.84)	0.061
Hypercholesterolaemia	-12.09 (-18.95 - -5.22)	0.001
Hypertension	-2.24 (-9.54 - 5.06)	0.547
	BT	
Serum BT	0.244 (-1.80 - 2.29)	0.815
Age	-0.799 (-1.11 - -0.487)	< 0.0001
Marital status	-6.51 (-10.70 - -2.31)	0.002
Waist circumference	-0.397 (-0.656 - -0.118)	0.005
HbA1c	-2.32 (-6.18 - 1.55)	0.24
Cigarette smoking	8.75 (1.81 - 15.70)	0.014
Medication, general health	-12.38 (-21.05 - -3.71)	0.005
Medication, urological	-48.84 (-69.17 - -28.51)	< 0.0001
	cBT	
cBT	-0.276 (-1.97 - 1.41)	0.748
Age	-0.746 (-1.06 - -0.433)	< 0.0001
Waist circumference	-0.375 (-0.651 - -0.099)	0.008

HbA1c	-3.41 (-7.51 - 0.692)	0.103
Cigarette smoking	9.13 (1.81 - 16.45)	0.015
Medication, general health	-15.29 (-24.40 - -6.17)	0.001
	FT	
FT	0.011 (-0.026 - 0.048)	0.56
Age	-0.819 (-1.13 - -0.51)	< 0.0001
Marital status	-6.55 (-10.82 - -2.29)	0.003
Waist circumference	-0.259 (-0.555 - 0.037)	0.086
HbA1c	-1.84 (-5.80 - 2.12)	0.362
Fasting serum insulin	-0.249 (-0.646 - 0.148)	0.218
Cigarette smoking	7.77 (0.808 - 14.74)	0.029
	SHBG	
SHBG	-0.245 (-0.509 - 0.019)	0.069
Age	-0.291 (-0.609 - 0.027)	0.073
Gross annual household income	4.61 (2.28 - 6.94)	< 0.0001
Waist circumference	-0.326 (-0.604 - -0.048)	0.021
Fasting serum total cholesterol	1.20 (-1.92 - 4.32)	0.451
Fasting HDL cholesterol	14.77 (3.19 - 26.35)	0.013
Fasting serum insulin	-0.092 (-0.456 - 0.272)	0.619
Angina	-20.90 (-37.11 - -4.68)	0.012
Hypercholesterolaemia	-10.33 (-18.56 - -2.10)	0.014
Medication; Met. Endo. Nut.	-1.94 (-12.46 - 8.57)	0.717

Table 5.2.9 Predictive models of serum testosterone and SHBG for limitations to usual role activities because of physical problems

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(13, 547) = 10.98$, $P < 0.0001$, $R^2 = 0.23$. BT model: $F(8, 559) = 17.05$, $P < 0.0001$, $R^2 = 0.18$. cBT model: $F(6, 561) = 13.45$, $P < 0.0001$, $R^2 = 0.14$. FT model: $F(7, 560) = 12.11$, $P < 0.0001$, $R^2 = 0.14$. SHBG model: $F(10, 550) = 12.53$, $P < 0.0001$, $R^2 = 0.20$.

	Total T	
	Coeff (95% CI)	P
Serum total T	-0.114 (-0.51 - 0.283)	0.574
Age	-0.099 (-0.333 - 0.135)	0.408
Gross annual household income	1.74 (-0.178 - 3.65)	0.075
DSS pension	6.82 (-0.176 -13.81)	0.056
Waist circumference	-0.224 (--0.408 - -0.04)	0.018
Fasting serum total triglycerides	-1.27 (-2.91 - 0.376)	0.13
Fasting HDL cholesterol	3.00 (-4.65 - 10.65)	0.441
Diabetes	-4.58 (-11.37 - 2.22)	0.185
Hypercholesterolaemia	-6.66 (-11.25 - -2.06)	0.005
	BT	
Serum BT	-0.734 (-1.72 - 0.249)	0.143
Age	-0.369 (-0.574 - -0.163)	< 0.0001
Waist circumference	-0.276 (-0.458 - -0.094)	0.003
Diabetes	-6.05 (-12.89 - 0.784)	0.083
Medication, general health	-10.82 (-16.64 - -5.01)	< 0.0001
Medication, urological	-18.52 (-37.29 - 0.255)	0.053
	cBT	
cBT	-0.42 (-1.80 - 0.963)	0.551
Age	-0.328 (-0.545 - -0.111)	0.003
Waist circumference	-0.257 (-0.441 - -0.074)	0.006
Diabetes	-6.40 (-13.18 - 0.374)	0.064
Medication, general health	-11.31 (-17.06 - -5.55)	< 0.0001
	FT	
FT	-0.003 (-0.027 - 0.021)	0.802
Age	-0.365 (-0.581 - -0.149)	0.001
Waist circumference	-0.203 (-0.399 - -0.007)	0.043
Fasting serum total triglycerides	-1.83 (-3.44 - -0.212)	0.027
Diabetes	-5.99 (-12.79 - 0.815)	0.084

	SHBG	
SHBG	-0.142 (-0.338 - 0.053)	0.154
Age	-0.098 (-0.329 - 0.132)	0.401
Gross annual household income	2.65 (1.07 - 4.23)	0.001
Waist circumference	-0.229 (-0.404 - -0.054)	0.01
Fasting serum total triglycerides	-1.59 (-3.34 - 0.17)	0.077
Fasting HDL cholesterol	3.39 (-4.36 - 11.13)	0.391
Angina	-11.59 (-20.47 - -2.70)	0.011
Hypercholesterolaemia	-5.72 (-10.92 - -0.507)	0.032
Medication; Met. Endo. Nut.	-0.556 (-6.35 - 5.24)	0.851

Table 5.2.10 Predictive models of serum testosterone and SHBG for bodily pain

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(9, 551) = 7.45$, $P < 0.0001$, $R^2 = 0.12$. BT model: $F(6, 561) = 7.78$, $P < 0.0001$, $R^2 = 0.11$. cBT model: $F(5, 562) = 8.62$, $P < 0.0001$, $R^2 = 0.10$. FT model: $F(5, 560) = 6.87$, $P < 0.0001$, $R^2 = 0.07$. SHBG model: $F(9, 551) = 8.51$, $P < 0.0001$, $R^2 = 0.13$.

DISCUSSION

In the present cohort, abdominal fat percentage was inversely associated with total testosterone and SHBG levels independent of age and demographic, behavioural risk factor, chronic disease and medication covariates. Supportingly, Van den Beld et al. (2000) reported similar inverse cross-sectional associations between total testosterone and total fat mass in 403 community dwelling men aged 73 – 94 years [224]. Denti et al. (2000) showed an age-independent, inverse association between SHBG and whole body fat percentage, estimated from four skinfold measurements using the Durnin-Wormsely and Siri equations in 206 healthy volunteers aged 18 – 95 years [57]. However, unlike the present study, Van den Beld et al. (2000) also reported inverse associations with free and bioavailable testosterone levels [224]. Moreover, in the same study, unlike the findings of the present study, both total and bioavailable testosterone were positively associated with muscle strength measured by handgrip dynamometry [224].

The percentage of whole body lean mass was positively associated with both serum total T and SHBG, independent of co-variates in the current cohort but neither maximal handgrip strength nor physical function were associated with serum testosterone or SHBG levels independent of age or other demographic, behavioural risk factor, chronic disease or medication covariates. In a longitudinal study it was shown that persons who have lost muscle mass, but remain obese (sarcopenic obesity), have an extremely high rate of future disability and death [263]. It has been previously shown that sarcopenia is strongly related to the loss of hormones, such as testosterone and IGF-1 and to mild increases in cytokines [264-266]. Other causes of sarcopenia include diminished neuronal input into muscle, decreased food intake (particularly protein and creatine), and peripheral vascular disease [267]. These results suggest that reduced total testosterone levels, increased chronic disease and medication use

with older age are critical factors in the occurrence of age related sarcopenia and functional decline. Changes in the IGF axis with ageing, although not supported by serum levels of IGF-1 in the current cohort, are likely to also play a role [267]. It is the decline in the muscle isoforms of IGF-1 (liver like and mechano-growth factor (MGF))[268] that are likely to contribute most to age-related sarcopenia. Moreover, age-related testosterone and growth hormone declines may lead to increased myostatin expression and dissociation in IGF-1 autocrine effects on protein synthesis in skeletal muscle [265]. The mechanism by which testosterone, growth hormone, IGF-1 and other growth factors interact with receptor activity and myostatin gene expression in aged skeletal muscle to influence muscle protein synthesis warrants further vigorous research.

The most notable associations with body composition, handgrip strength and physical function were with clinical and laboratory indicators of metabolic disease such as blood pressure and fasting serum lipids, glucose and insulin levels. In addition, lower daily dietary intakes of fat and protein were associated with lower lean body mass and weaker handgrip strength, respectively but not with higher abdominal fat. With ageing there is a physiological anorexia that is associated with weight loss. The causes of the anorexia of ageing are multi-factorial and include reduced physical activity, depression [269, 270], alterations in taste and smell, medications, hormonal changes and alterations in stomach satiation signals and [271]. With ageing there is a decrease in adaptive relaxation of the fundus of the stomach due to a decline in nitric oxide synthase, causing early antral filling and increased satiation [272]. Moreover, basal and fat-stimulated levels of cholecystokinin (CCK) are elevated in older age [273] and have greater effects on decreasing appetite than in younger persons [274]. The decline in testosterone levels with ageing in males leads to elevated serum leptin [60] that is reversible with testosterone replacement [3]. These mechanisms of age-associated anorexia are major causes of sarcopenic weight loss, increased frailty, functional decline and premature morbidity and mortality.

In the present cohort, whole body lean mass, handgrip strength and physical function followed reported trends with demographics such as age, income and education level [174]. There were few surprising associations of whole body lean mass and abdominal fat percentage with disease risk factors and behaviours. Most surprising was a lack of association with physical activity level. Participants were classified as “sedentary”, “insufficiently active” or sufficiently active” in terms of a level of physical activity required to benefit health. This level of classification may not have been sufficiently sensitive to detect, what may be a weak association. The physical activity level required to benefit health is controversial and the assessment of physical activity level by questionnaire is problematic [275].

Metabolic disease appears to be a common factor in predicting unfavourable body composition, lower handgrip strength and reduced physical function. Serum total T and SHBG independently and inversely predict both the percentage of total lean body and abdominal fat mass. The age-related decline in gonadal axis activity likely influences the production and activity of other hormones and growth factors such as IGF-1, growth hormone and leptin and their interation with recptors and target genes resulting in perturbations in tissue composistion of the body. The interaction of these hormone and growth factor pathways in regulating target gene expression, particularly in skeletal muscle and adipose tissue, is of great interest and will lead to a better understanding of age-associated sarcopenia and frailty and the potential for targeted gene therapy.

5.3 ERECTILE FUNCTION & SEXUAL DESIRE: ASSOCIATIONS WITH AGE AND PLASMA TESTOSTERONE LEVELS.

SUMMARY

This chapter describes the associations with erectile dysfunction and sexual desire of the various measures of serum testosterone and SHBG. Data were from the FAMAS as described in Chapter 4.0. All measures of erectile function and sexual desire decreased with increasing age. In age adjusted analyses, lower sexual desire but not poorer erectile function or self-reported ED were associated with lower serum testosterone levels. In multi-variate models older age, lower household income, diabetes, hypertension and a higher probability of OSA were independently associated with the presence and degree of ED. Older age, lower household income, being widowed or never married and taking urological medication were independently associated with poorer erectile function. Older age, being widowed or never married, lower household income, lower daily alcohol intake, having a respiratory health condition and taking urological medication were independently associated with lower sexual desire. Older age, lower household income, being a non-smoker, lower daily alcohol intake and having a respiratory health condition were independently associated with lower dyadic sexual desire. Older age and taking urological medication were independently associated with lower dyadic sexual desire. Neither waist circumference greater than 102 cm, nor BMI ≥ 30 kg/m^2, significantly predicted presence or severity of ED. The present study demonstrates, perhaps for the first time, a convincing cross-sectional association between measures of serum testosterone and level of sexual desire after adjusting for inter-related socio-demographic variables, disease status and medication use. Many other independent associations with lower sexual desire and poorer erectile function were also demonstrated

in this study, which highlights the multi-dimensional biological, psychological, pharmacological and sociological nature of sexual dysfunction.

INTRODUCTION

The prevalence of ED is difficult to estimate due to the assumed underreporting of the problem. Various age-dependent estimates have been made from population based studies both in Australia and overseas [276-278]. Data on the incidence of ED are scarce. In the absence of significant hypogonadism, T treatment does not have an effect on erectile function, but does improve the response to sildenafil (Viagra). In animal studies, androgen deprivation alters the functional responses and structure of erectile tissue [279]. Factors that may be associated with both ED, and low T levels include determinants of health (age, education, occupation, ethnicity), behavioural and lifestyle (quality of life, alcohol intake, smoking, diet and physical activity), clinical (diabetes, heart disease, hypertension and drug therapies), and psychological factors including depression and anxiety [278, 280]. There is a strong positive relationship between ED and cardiovascular risk factors (identifying men who decrease their risk of cardiovascular disease may benefit erectile function [278]) and depression (the probability of ED is approximately 90% in men with severe depression but only 25% in men with mild depression [280]). The causal relationship is unclear [281]. A longitudinal study of the evolution of ED, associated factors and co-morbidities, particularly in an Australian context is required and the Florey Adelaide Male Ageing Study will provide this much needed data.

Sexual desire is believed to be closely associated with testosterone. An association between sexual desire and BT levels in both healthy men and in men with ED has been reported in some but not all studies [78-80]. The rate of change of T levels, and interaction with other factors such as physical and emotional health, lifestyle, and socio-economic status in the aetiology of disorders of desire, has not been determined.

LUTS and ED are strongly associated with ageing. Numerous small epidemiological studies have postulated an association between the two conditions but they have failed to show a direct relationship after the effect of ageing has been accounted for. A recently published study with centres in the United Kingdom (Birmingham), The Netherlands (Boxmeer), France (Auxere) and Korea (Seoul) reported that men with an IPSS score of 8 – 35 were more likely to have ED, based on a score of 0 – 4 on the Sexual Function Inventory of O'Leary et al. (Urology 1995) after adjusting for age and country (OR 1.39, 95% CI 1.10 – 1.74) [282]. Men with diabetes (OR 1.57, 95% CI 1.09 – 2.25) and high blood pressure (OR 1.38, 95% CI 1.09 – 1.75) were also more likely to have an ED score of 0 – 4.

MATERIALS AND METHODS

PARTICIPANT SELECTION

Participants were male volunteers (N = 568), living in the North and West suburbs of Adelaide and recruited at random from the EWP's as described in Chapter 4.0.

MEASUREMENTS

All assessments were performed according to the methods described in Chapter 4.0. Specifically, ED was assessed by questionnaire using the GIR and the erectile function (EF) domain of the IIEF as described in Chapter 4.0. Dyadic and solitary sexual desire was assessed by questionnaire using the SDI-2 and non-discriminant sexual desire by the desire domain of the IIEF as described in chapter 4.0. Morning blood samples were obtained and assayed for total T and SHBG and FAI and FT were calculated, as described in Chapter 4.0. BT was measured and cBT calculated as described in Chapter 3.0.

The frequency and volume of cigarette smoking, exercise and alcohol intake and the daily dietary intake of energy, fat, carbohydrate and protein was assessed by questionnaire as described in Chapter 4.0. Chronic disease included but was not limited to depression, diabetes, hypertension, hypercholesterolaemia, BPH, and prostate cancer and current medications were determined by self-report. History of surgical procedures including prostatectomy, trans-urethral resection of prostate (TURP) and other urogenital surgery was obtained by questionnaire as described in Chapter 4.0.

STATISTICAL ANALYSES

Stratified and probability weighted simple linear regression was performed to assess the associations of age and plasma T levels with erectile function and sexual desire. Multiple linear regression analysis, using the same strata and probability weighting was used to control for confounding in the associations of plasma T levels with erectile function and sexual desire. Stratified and probability weighted ordinal logistic regression was performed to determine the association between degrees of ED reported on the GIR and plasma T levels.

All associations were then adjusted for age linear regression with age as a continuous variable.

Multiple linear regression analysis was used to account for confounding variables, considered to be variables that related to both the measure of plasma T of interest and the outcome variable at a level of $P < 0.05$. For multiple linear regression analysis the regression coefficient and 95% confidence intervals (CI's) are reported. All analyses were performed on stratified and probability weighted data as described in Chapter 4.0.

Post-hoc, chi-squared analyses were performed to assess the ability of obesity (waist circumference > 90 cm or BMI ≥ 30 kg/m^2) to predict the presence and severity of erectile dysfunction, as measured by GIR. All analyses were performed on stratified and probability weighted data as described in Chapter 4.0.

RESULTS

DEMOGRAPHICS

Erectile function

Five hundred and sixty men completed the GIR. The proportion of men reporting no ED, mild, moderate and severe ED by age group, school-leaving age, post-secondary qualifications, annual gross household income and work status, DSS pension, marital status and country of birth are shown in Appendix VI (Table VI.I). Overall, 52% (N = 297) of men reported at least some degree of ED. ED severity, as determined by GIR, was positively associated with age (Table 5.3.2). In age-adjusted analyses, greater severity of ED was associated with lower gross annual household income, being unemployed or retired and being born in countries other than Australia and the UK (Table 5.3.2).

Five hundred and sixty men completed the erectile function domain of the IIEF. Mean erectile function scores on the IIEF are shown in Appendix VI (Table VI.II) by age group, school-leaving age, post-secondary qualifications, annual gross household income and work status, DSS pension, marital status and country of birth. Erectile function, as determined by IIEF, was inversely associated with age (Table 5.3.2). In age-adjusted analyses, poorer erectile function was associated with lower gross annual household income, being unemployed or retired and being widowed or never married (Table 5.3.2).

	GIR	
	Coeff (95% CI)	P
Age	0.047 (0.041 - 0.053)	< 0.0001
Gross annual household income	-0.079 (-0.132 - -0.027)	0.003
Work status	0.12 (0.01 - 0.24)	0.033
Country of birth	0.10 (0.002 - 0.197)	0.046
	IIEF_EF	
Age	-0.035 (-0.41 - -0.29)	< 0.0001
Gross annual household income	1.21 (0.67 - 1.75)	< 0.0001
Work status	-1.71 (-2.82 - -0.59)	0.003
Marital status	-2.68 (-3.57 - -1.80)	< 0.0001

Table 5.3.1 Significant age-adjusted associations of demographics with severity of erectile dysfunction, as measured by GIR and erectile function, as measured by IIEF

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

Sexual desire

Five hundred and sixty-two men successfully completed the sexual desire domain of the IIEF and 547 men successfully completed all questions on the SDI-2 so that dyadic and solitary sexual desire scores could be obtained. Mean sexual desire scores on the IIEF, dyadic and solitary sexual desire scores from

the SDI-2, are shown by age group, school-leaving age, post-secondary qualifications, annual gross household income, and work status, DSS pension, marital status and country of birth in Appendix VI (Tables VI.III – VI.V). Sexual desire, as measured by the IIEF, was inversely associated with age (Table 5.3.2). In age-adjusted analyses, lower sexual desire was associated with lower gross annual household income, being unemployed or retired, being widowed or never married and receiving a DSS pension (Table 5.3.3). Lower dyadic sexual desire was associated with older age, lower gross annual household income and receiving a DSS pension (Table 5.3.2). Lower solitary sexual desire was associated with older age and lower level of education as estimated by highest post-school qualification (Table 5.3.2).

	IIEF_SD	
	Coeff (95% CI)	P
Age	-0.079 (-0.093 - -0.065)	< 0.0001
Gross annual household income	0.14 (0.01 - 0.28)	0.034
Work status	-0.28 (-0.55 - -0.017)	0.037
DSS pension	0.548 (0.078 - 1.019)	0.022
Marital status	-0.218 (-0.42 - -0.015)	0.035
	Dyadic SD (SDI-2)	
Age	-0.567 (-0.66 - -0.47)	< 0.0001
Gross annual household income	0.845 (0.097 - 1.59)	0.027
DSS pension	3.53 (0.598 - 6.46)	0.018
	Solitary SD (SDI-2)	
Age	-0.16 (-0.20 - -0.12)	< 0.0001
Highest post-school qualification	0.91 (0.004 - 1.81)	0.049

Table 5.3.2 Significant age-adjusted associations of demographics with sexual desire, as measured by IIEF and SDI-2

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

CHRONIC DISEASE RISK FACTORS AND BEHAVIOURS

Erectile function

The non-age-adjusted associations of chronic disease risk factors and lifestyle behaviours with severity of erectile dysfunction, as determined by the GIR are shown in Appendix VI (Tables VI.VI & VI.VII). In age-adjusted analyses, greater erectile dysfunction severity, as determined by the GIR, was associated with higher systolic blood pressure and HbA1c (Table 5.3.3).

The non-age-adjusted associations of chronic disease risk factors and lifestyle behaviours with erectile function, as determined by the IIEF are shown in Appendix VI (Tables VI.VIII & VI.IX). In age-adjusted analyses, poorer erectile function, as determined by IIEF, was associated with lower fasting serum total and LDL cholesterol levels and higher glucose and HbA1c (Table 5.3.3).

Sexual desire

The non-age-adjusted associations of chronic disease risk factors and lifestyle behaviours with sexual desire, as determined by the IIEF are shown in Appendix VI (Tables VI.X & VI.XI). In age-adjusted analyses, lower sexual desire was associated only with lower daily alcohol intake (Table 5.3.4).

The non-age-adjusted associations of chronic disease risk factors and lifestyle behaviours with dyadic and solitary sexual desire, as determined by the SDI-2 are shown in Appendix VI (Tables VI.XII – VI.XV). In age-adjusted analyses, lower dyadic sexual desire was associated with lower daily alcohol intake and cigarette smoking (Table 5.3.4). There were no age-independent associations with solitary sexual desire.

	GIR	
	Coeff (95% CI)	P
Systolic blood pressure	0.006 (0.002 - 0.011)	0.006
HbA1c	0.16 (0.049 - 0.265)	0.004
	IIEF_EF	
Total cholesterol	0.62 (0.018 - 1.22)	0.043
LDL cholesterol	0.85 (0.185 - 1.52)	0.012
Fasting serum glucose	-0.88 (-1.54 - -0.23)	0.008
HbA1c	-1.20 (-2.07 - -0.34)	0.006

Table 5.3.3 Significant age-adjusted associations of chronic disease risk factors with erectile dysfunction, as measured by the GIR and erectile function, as measured by IIEF

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

	IIEF_SD	
	Coeff (95% CI)	P
Daily alcohol intake	0.008 (0.001 - 0.015)	0.02
	Dyadic SD (SDI-2)	
Daily alcohol intake	0.054 (0.009 - 0.10)	0.018
Cigarette smoking	2.64 (0.62 - 4.66)	0.01
	Solitary SD (SDI-2)	
No significant age-adjusted associations		

Table 5.3.4 Significant age-adjusted associations of chronic disease risk factors with sexual desire, as measured by the IIEF and SDI-2

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

CHRONIC DISEASE, SURGICAL PROCEDURES AND MEDICATIONS

Erectile function

In age-adjusted analyses, greater severity of erectile dysfunction was associated with having angina, diabetes, high blood pressure, a higher probability of obstructive sleep apnoea, having had bladder surgery and taking medications for conditions of the circulatory system (Table 5.3.5).

In age-adjusted analyses, poorer erectile function was associated with having angina, diabetes, high blood pressure, insomnia, a higher probability of obstructive sleep apnoea and taking medications for digestive, psychological and urinary health conditions (Table 5.3.6).

	GIR	
	Coeff (95% CI)	P
Angina	0.37 (0.007 - 0.741)	0.045
Diabetes	0.62 (0.33 - 0.91)	< 0.0001
Hypertension	0.29 (0.12 - 0.47)	0.001
Probability of OSA	0.39 (0.11 - 0.67)	0.007
Bladder surgery	0.56 (0.03 - 1.09)	0.037
Medication, circulatory	0.33 (0.12 - 0.55)	0.002

Table 5.3.5 Significant age-adjusted associations of chronic disease, urogenital surgery and medication use with erectile dysfunction, as measured by GIR

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

	IIEF_EF	
	Coeff (95% CI)	P
Angina	-4.03 (-7.27 - -0.79)	0.015
Diabetes	-4.17 (-6.61 - -1.73)	0.001
Hypertension	-2.25 (-4.00 - -0.51)	0.012
Insomnia	-3.78 (-6.22 - -1.33)	0.003
Probability of OSA	-3.40 (-6.39 - -0.41)	0.025
Medication, digestive	-2.71 (-4.71 - -0.70)	0.008
Medication, psychological	-3.42 (-5.96 - -0.87)	0.009
Medication, urological	-7.23 (-11.27 - -3.20)	< 0.0001

Table 5.3.6 Significant age-adjusted associations of chronic disease, urogenital surgery and medication use with erectile function, as measured by IIEF

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

Sexual desire

In age-adjusted analyses, lower sexual desire was associated with having a thyroid disorder, a respiratory health condition and with taking medications for digestive and urinary health conditions (Table 5.3.7).

In age-adjusted analyses, lower dyadic sexual desire was associated with not having had penile surgery and with having, and taking medication for, a respiratory health condition (Table 5.3.7). Lower solitary sexual desire scores were associated with not having had penile surgery, not having a psychological health condition, having had a prostatectomy and taking medication for a urological condition (Table 5.3.7).

	IIEF_SD	
	Coeff (95% CI)	P
Thyroid disorder	-0.76 (-1.53 - -0.001)	0.05
Health conditon, respiratory	-0.87 (-1.59 - -0.158)	0.017
Medication, digestive	-0.56 (-1.01 - -0.10)	0.017
Medication, urological	-1.55 (-2.66 - -0.44)	0.006
	Dyadic SD (SDI-2)	
Penile surgery	4.68 (0.24 - 9.12)	0.039
Health conditon, respiratory	-5.78 (-10.36 - -1.20)	0.014
Medication, respiratory	-3.16 (-6.29 - -0.04)	0.047
	Solitary SD (SDI-2)	
Prostate removal	-2.06 (-3.15 - -0.97)	< 0.0001
Penile surgery	5.03 (1.78 - 8.28)	0.002
Health conditon, psychological	2.74 (0.17 - 5.31)	0.035
Medication, urological	-2.95 (-4.95 - -0.95)	0.004

Table 5.3.7 Significant age-adjusted associations of chronic disease, urogenital surgery and medication use with sexual desire, as measured by IIEF and SDI-2

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

SERUM TESTOSTERONE

Erectile function

In age-adjusted analyses, greater severity of erectile dysfunction, as determined by the GIR and poorer erectile function, as determined by IIEF, were not associated with any measure of serum testosterone or SHBG.

Sexual desire

In age-adjusted analyses, sexual desire, as determined by IIEF, was positively associated with BT, cBT and FT. Dyadic sexual desire was positively associated with total T and FT and solitary sexual desire was positively associated with all measures of serum testosterone (Table 5.3.8).

	IIEF_SD	
	Coeff (95% CI)	P
BT	0.09 (0.02 - 0.16)	0.009
cBT	0.10 (0.02 - 0.18)	0.01
FT	0.002 (0.001 - 0.003)	0.003
	Dyadic SD (SDI-2)	
Total T	0.18 (0.02 - 0.34)	0.025
FT	0.01 (0.002 - 0.02)	0.017
	Solitary SD (SDI-2)	
Total T	0.10 (0.01 - 0.18)	0.027
BT	0.34 (0.17 - 0.51)	< 0.0001
cBT	0.40 (0.21 - 0.59)	< 0.0001
FT	0.007 (0.003 - 0.01)	< 0.0001

Table 5.3.8 Significant age-adjusted associations of serum testosterone concentration with sexual desire, as measured by IIEF and SDI-2

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

MULTIVARIATE PREDICTIVE MODELS FOR ED

Erectile dysfunction, GIR

All testosterone and SHBG models significantly predicted 37% – 41% of the heterogeneity in the presence and severity of ED. However no measure of serum testosterone or SHBG was independently associated with the presence and severity of ED as determined by the GIR (Table 5.3.9). Older age, lower household income, diabetes, hypertension and a higher probability of OSA were independently associated with the presence and degree of ED. Similarly, a predictive model including all age-independent factors associated with the presence and severity of ED, as determined by GIR, significantly predicted 42% of the heterogeneity in ED severity. Older age, lower household income, being born in a country other than Australia and the UK, higher systolic blood pressure and diabetes were independently associated with the presence and severity of ED (Table 5.3.10).

Erectile function, IIEF

All testosterone and SHBG models significantly predicted 27% - 36% of the heterogeneity in erectile function. However, no measure of serum testosterone or SHBG was independently related to erectile function as determined by the IIEF (Table 5.3.11). Older age, lower household income, being widowed or never married and taking urological medication were independently associated with poorer erectile function. Additionally, in the SHBG model, higher fasting serum glucose level was independently associated with poorer erectile function (Table 5.3.11). Similarly, a predictive model including all age-independent factors associated with the erectile function, as determined by IIEF, significantly predicted 39% of the heterogeneity in erectile function. Older age, lower household income, being widowed or

never married and taking medication for digestive and urological health conditions were independently associated with poorer erectile function (Table 5.3.12).

	Total T model	
	Coeff (95% CI)	P
Total T	-0.004 (-0.017 - 0.01)	0.588
Age	0.034 (0.026 - 0.042)	< 0.0001
Gross annual household income	-0.077 (-0.129 - -0.025)	0.004
Systolic blood pressure	0.004 (0.0004 - 0.009)	0.06
HbA1c	0.023 (-0.096 - 0.142)	0.705
Proabability of OSA	0.131 (-0.17 - 0.432)	0.394
Diabetes	0.508 (0.141 - 0.874)	0.007
Hypertension	0.208 (0.034 - 0.382)	0.019
	BT model	
BT	-0.007 (-0.055 - 0.041)	0.775
Age	0.043 (0.035 - 0.05)	< 0.0001
HbA1c	0.053 (-0.076 - 0.181)	0.42
Diabetes	0.531 (0.168 - 0.893)	0.004
	cBT model	
cBT	0.001 (-0.043 - 0.045)	0.968
Age	0.043 (0.036 - 0.05)	< 0.0001
HbA1c	0.055 (-0.074 - 0.184)	0.399
Diabetes	0.531 (0.167 - 0.894)	0.004
	FT model	
FT	-0.0002 (-0.0009 - 0.0006)	0.678

Diabetes	0.533 (0.165 - 0.902)	0.005
Proabability of OSA	0.281 (0.001 - 0.561)	0.049
	SHBG model	
SHBG	0.003 (-0.002 - 0.008)	0.261
Age	0.038 (0.031 - 0.046)	< 0.0001
Gross annual household income	-0.07 (-0.122 - -0.018)	0.009
Angina	0.343 (-0.015 - 0.70)	0.06
Proabability of OSA	0.368 (0.078 - 0.658)	0.013

Table 5.3.9 Multivariate associations of serum testosterone and SHBG concentrations with severity of erectile dysfunction, as measured by GIR,

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(8, 544) = 43.96$, $P < 0.0001$, $R^2 = 0.41$. BT model: $F(4, 553) = 67.87$, $P < 0.0001$, $R^2 = 0.38$. cBT model: $F(4, 553) = 67.50$, $R^2 = 0.38$. FT model: $F(5, 552) = 57.52$, $P < 0.0001$, $R^2 = 0.38$. SHBG model: $F(5, 547) = 50.85$, $P < 0.0001$, $R^2 = 0.37$.

	GIR	
	Coeff (95% CI)	P
Age	0.031 (0.022 - 0.04)	< 0.0001
Gross annual household income	-0.064 (-0.117 --0.012)	0.017
Work status	0.031 (-0.09 - 0.153)	0.611
Country of birth	0.094 (0.003 - 0.185)	0.044
Systolic blood pressure	0.005 (0.00004 - 0.009)	0.048
HbA1c	0.021 (-0.098 - 0.14)	0.727
Angina	0.173 (-0.189 - 0.534)	0.348
Diabetes	0.449 (0.084 - 0.813)	0.016
Hypertension	0.163 (-0.052 - 0.377)	0.137
Probability of OSA	0.122 (-0.164 -0.407)	0.403
Bladder surgery	0.466 (-0.104 - 1.035)	0.109
Medication, circulatory	0.099 (-0.164 - 0.363)	0.46

Table 5.3.10 Multivariate predictive model of erectile dysfunction severity, as measured by GIR, in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: $F(12, 540) = 31.74$, $P < 0.0001$, $R^2 = 0.42$.

	Total T model	
	Coeff (95% CI)	P
Total T	0.089 (-0.027 - 0.204)	0.131
Age	-0.298 (-0.366 - -0.230)	< 0.0001
Gross annual household income	0.727 (0.246 - 1.208)	0.003
Marital status	-2.22 (-3.14 - -1.31)	< 0.0001
Fasting serum glucose	-0.415 (-1.26 - 0.435)	0.338
HbA1c	0.132 (-1.06 - 1.32)	0.828
Fasting serum total cholesterol	1.49 (-0.385 - 3.36)	0.119
Fasting serum LDL cholesterol	-1.03 (-3.05 - 0.988)	0.316
Diabetes	-1.90 (-5.15 - 1.34)	0.25
Hypertension	-1.31 (-3.09 - 0.473)	0.149
Proabability of OSA	-1.06 (-4.04 - 1.92)	0.484
	BT model	
BT	0.186 (-0.258 - 0.631)	0.41
Age	-0.34 (-0.409 - -0.272)	< 0.0001
Marital status	-2.70 (-3.59 - -1.80)	< 0.0001
Fasting serum glucose	-0.436 (-1.22 - 0.347)	0.275
HbA1c	0.009 (-1.18 - 1.20)	0.988
Diabetes	-2.40 (-5.33 - 0.54)	0.109
Medication, urological	-7.71 (-12.04 - -3.38)	0.001
	cBT model	
cBT	0.143 (-0.255 - 0.541)	0.48
Age	-0.314 (-0.385 - -0.242)	< 0.0001
Fasting serum glucose	-0.496 (-1.32 - 0.329)	0.238
HbA1c	-0.073 (-1.37 - 1.23)	0.912
Diabetes	-3.04 (-6.12 - 0.031)	0.052

	FT model	
FT	0.006 (-0.002 - 0.014)	0.134
Age	-0.323 (-0.389 - -0.257)	< 0.0001
Marital status	-2.66 (-3.58 - -1.74)	< 0.0001
Fasting serum glucose	-0.367 (-1.146 - 0.412)	0.355
HbA1c	0.107 (-1.077 - 1.291)	0.859
Diabetes	-2.59 (-5.52 - 0.35)	0.084
Proabability of OSA	-1.39 (-4.28 - 1.50)	0.344
	SHBG model	
SHBG	-0.036 (-0.082 - 0.011)	0.131
Age	-0.267 (-0.346 - -0.189)	< 0.0001
Gross annual household income	0.968 (0.437 - 1.50)	< 0.0001
Fasting serum total cholesterol	0.917 (-1.06 - 2.89)	0.362
Fasting serum LDL cholesterol	-0.531 (-2.64 - 1.58)	0.621
Fasting serum glucose	-0.782 (-1.47 - -0.095)	0.026
Angina	-3.15 (-6.55 - 0.24)	0.069

Table 5.3.11 Multivariate associations of serum testosterone and SHBG concentrations with erectile function, as measured by IIEF,

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(11, 512) = 26.48$, $P < 0.0001$, $R^2 = 0.36$. BT model: $F(7, 550) = 47.48$, $P < 0.0001$, $R^2 = 0.34$. cBT model: $F(5, 552) = 34.43$, $P < 0.0001$, $R^2 = 0.27$. FT model: $F(7, 550) = 42.78$, $P < 0.0001$, $R^2 = 0.34$. SHBG model: $F(7, 516) = 28.78$, $P < 0.0001$, $R^2 = 0.32$.

	IIEF_EF	
	Coeff (95% CI)	P
Age	-0.288 (-0.359 - -0.218)	< 0.0001
Gross annual household income	0.539 (0.014 - 1.064)	0.044
Work status	-0.092 (-1.128 - 1.035)	0.873
Marital status	-2.202 (-3.12 - -1.28)	< 0.0001
Fasting serum total cholesterol	1.25 (-0.531 - 3.03)	0.169
Fasting serum LDL cholesterol	-0.985 (-2.89 - 0.917)	0.309
Fasting serum glucose	-0.397 (-1.23 - 0.438)	0.35
HbA1c	0.022 (-1.15 - 1.19)	0.971
Angina	-1.94 (-5.35 - 1.47)	0.263
Diabetes	-1.17 (-4.41 - 2.08)	0.48
Hypertension	-1.04 (-2.81 - 0.723)	0.246
Insomnia	-1.90 (-4.17 - 0.368)	0.1
Probability of OSA	-1.14 (-3.96 - 1.68)	0.429
Medication, digestive	-2.68 (-4.56 - -0.80)	0.005
Medication, psychological	-1.05 (-3.57 - 1.46)	0.412
Medication, urological	-6.66 (-10.88 - -2.43)	0.002

Table 5.3.12 Multivariate predictive model of erectile function, as measured by IIEF, in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: $F(16, 507) = 23.99$, $P < 0.0001$, $R^2 = 0.39$.

MULTIVARIATE PREDICTIVE MODELS FOR SEXUAL DESIRE

Sexual desire, IIEF_SD

All testosterone and SHBG models significantly predicted 24% – 27% of the heterogeneity in level of sexual desire. All measures of serum testosterone, but not SHBG, were independently and positively associated with sexual desire as determined by IIEF (Table 5.3.13). Older age, being widowed or never married, lower household income, lower daily alcohol intake, having a respiratory health condition and taking urological medication were independently associated with lower sexual desire (Table 5.3.13).

Dyadic sexual desire, SDI-2

All testosterone and SHBG models significantly predicted 27% – 30% of the heterogeneity in level of dyadic sexual desire. Total and free testosterone, but not BT, cBT or SHBG, were independently and positively associated with dyadic sexual desire as determined by SDI-2 (Table 5.3.14). Older age, lower household income, being a non-smoker, lower daily alcohol intake and having a respiratory health condition were independently associated with lower dyadic sexual desire (Table 5.3.14).

Solitary sexual desire, SDI-2

All testosterone and SHBG models significantly predicted 12% – 14% of the heterogeneity in level of solitary sexual desire. All measures of serum testosterone, but not SHBG, were independently and positively associated with solitary sexual desire as determined by SDI-2 (Table 5.3.15). Older age and taking urological medication were independently associated with lower dyadic sexual desire (Table 5.3.15).

	Total T model	
	Coeff (95% CI)	P
Total T	0.033 (0.006 - 0.06)	0.018
Age	-0.065 (-0.083 - -0.047)	< 0.0001
Marital status	-0.197 (-0.405 - -0.012)	0.064
Gross annual household income	0.036 (-0.113 - 0.185)	0.64
DSS pension	0.51 (-0.013 - 1.034)	0.056
Health condition, respiratory	-0.90 (-1.57 - -0.22)	0.009
	BT model	
BT	0.089 (0.017 - 0.161)	0.015
Age	-0.072 (-0.087 - -0.057)	< 0.0001
Marital status	-0.275 (-0.474 - -0.076)	0.007
Daily alcohol intake	0.007 (0.0004 - 0.014)	0.038
Medication, urological	-1.47 (-2.63 - -0.32)	0.012
	cBT model	
cBT	0.10 (0.02 - 0.18)	0.01
Age	-0.07 (-0.086 - -0.056)	< 0.0001
	FT model	
FT	0.002 (0.0008 - 0.003)	0.002
Age	-0.072 (-0.0.087 - 0.057)	< 0.0001
Marital status	-0.255 (-0.458 - -0.052)	0.014
	SHBG model	
SHBG	-0.008 (-0.02 - 0.003)	0.148
Age	-0.07 (-0.09 - -0.05)	< 0.0001
Gross annual household income	0.134 (0.002 - 0.266)	0.047

Table 5.3.13 Multivariate associations of serum testosterone and SHBG concentrations with sexual desire, as measured by IIEF,

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(6, 550) = 27.49$, $P < 0.0001$, $R^2 = 0.27$. BT model: $F(5, 556) = 32.99$, $P < 0.0001$, $R^2 = 0.27$. cBT model: $F(2, 559) = 68.47$, $P < 0.0001$, $R^2 = 0.24$. FT model: $F(3, 558) = 51.11$, $P < 0.0001$, $R^2 = 0.26$. SHBG model: $F(3, 553) = 41.10$, $P < 0.0001$, $R^2 = 0.25$.

	Total T model	
	Coeff (95% CI)	P
Total T	0.277 (0.109 - 0.445)	0.001
Age	-0.47 (-0.58 - -0.36)	< 0.0001
Gross annual household income	-0.30 (-0.57 - -1.17)	0.5
DSS pension	3.26 (-0.14 - 6.67)	0.06
Cigarette smoking	2.61 (0.64 - 4.58)	0.01
Health condition, respiratory	-6.07 (-10.16 - -1.99)	0.004
	BT model	
BT	0.414 (-0.057 - 0.886)	0.085
Age	-0.527 (-0.632 - -0.422)	< 0.0001
Daily alcohol intake	0.052 (0.008 - 0.096)	0.021
Cigarette smoking	2.96 (0.95 - 4.97)	0.004
	cBT model	
cBT	0.457 (-0.028 - 0.942)	0.065
Age	-0.542 (-0.645 - -0.438)	< 0.0001
Cigarette smoking	2.83 (0.798 - 4.856)	0.006
	FT model	
FT	0.012 (0.003 - 0.02)	0.01
Age	-0.527 (-0.63 - -0.42)	< 0.0001
Cigarette smoking	3.08 (1.03 - 5.14)	0.003
	SHBG model	
SHBG	-0.001 (-0.08 - 0.077)	0.975

Gross annual household income	0.844 (0.094 - 1.59)	0.027

Table 5.3.14 Multivariate associations of serum testosterone and SHBG concentrations with dyadic sexual desire, as measured by SDI-2,

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(6, 540) = 28.64$, $P < 0.0001$, $R^2 = 0.30$. BT model: $F(4, 547) = 39.71$, $P < 0.0001$, $R^2 = 0.28$. cBT model: $F(3, 548) = 48.80$, $P < 0.0001$, $R^2 = 0.28$. FT model: $F(3, 548) = 50.39$, $P < 0.0001$, $R^2 = 0.28$. SHBG model: $F(3, 543) = 45.76$, $P < 0.0001$, $R^2 = 0.27$.

	Total T model	
	Coeff (95% CI)	P
Total T	0.096 (0.011 - 0.18)	0.027
Age	-0.154 (-0.196 - -0.113)	< 0.0001
	BT model	
BT	0.335 (0.164 - 0.505)	< 0.0001
Age	-0.134 (-0.176 - -0.091)	< 0.0001
Medication, urological	-2.66 (-4.51 - -0.81)	0.005
	cBT model	
cBT	0.399 (0.208 - 0.590)	< 0.0001
Age	-0.132 (-0.178 - -0.089)	< 0.0001
	FT model	
FT	0.007 (0.003 - 0.01)	< 0.0001
Age	-0.133 (-0.176 - -0.09)	< 0.0001
	SHBG model	
SHBG	-0.008 (-0.046 - 0.03)	0.664
Age	-0.16 (-0.205 - -0.115)	< 0.0001

Table 5.3.15 Multivariate associations of serum testosterone and SHBG concentrations with solitary sexual desire, as measured by SDI-2,

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(2, 559) = 32.13$, $P < 0.0001$, $R^2 = 0.13$. BT model: $F(3, 558) = 24.90$, $P < 0.0001$, $R^2 = 0.14$. cBT model: $F(2, 559) = 38.97$, $P < 0.0001$, $R^2 = 0.14$. FT model: $F(2, 559) = 36.95$, $P < 0.0001$, $R^2 = 0.14$. SHBG model: $F(2, 559) = 31.07$, $P < 0.0001$, $R^2 = 0.12$.

POST-HOC CHI-SQUARED ASSOCIATIONS BETWEEN OBESITY AND ERECTILE DYSFUNCTION

The absence of a linear association between waist circumference and erectile dysfunction was surprising. Therefore, the ability of waist circumference greater than 102 cm and also BMI greater than or equal to 30 kg/m^2, in predicting the presence and severity of ED, as measured by GIR was assessed using Chi^2 analyses. Neither waist circumference greater than 102 cm, nor BMI ≥ 30 kg/m^2, significantly predicted the presence or severity of erectile dysfunction (Table 5.3.16).

	GIR	
	No ED	Mild/Mod/Severe ED
Waist ≤102 cm	0.313	0.309
Waist > 102 cm	0.183	0.196
	$Chi^2 = 0.22$	P = 0.66
BMI < 30 kg/m^2	0.344	0.323
BMI ≥ 30 kg/m^2	0.151	0.182
	$Chi^2 = 1.86$	P = 0.20

	GIR			
	No ED	Mild ED	Moderate ED	Severe ED
Waist ≤102 cm	0.341	0.157	0.072	0.048
Waist > 102 cm	0.182	0.101	0.062	0.038
			$Chi^2 = 4.24$	P = 0.26
BMI < 30 kg/m^2	0.356	0.171	0.086	0.053
BMI ≥ 30 kg/m^2	0.167	0.087	0.048	0.033
			$Chi^2 = 1.00$	P = 0.81

Table 5.3.16 Chi-squared associations of waist circumference > 102 cm and BMI ≥ 30 kg/m^2 with presence and severity of erectile dysfunction, as measured by GIR,

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

DISCUSSION

This chapter describes the association with erectile dysfunction and sexual desire of the various measures of serum testosterone and SHBG. This chapter aimed to determine if circulating testosterone levels contributed to the level of erectile function and sexual desire on a continuous scale and also to the self-reported degree of ED (no ED, mild, moderate or severe ED).

All measures of testosterone and were independently associated with the level of non-discriminate and solitary sexual desire; only total and free testosterone were independently associated with dyadic sexual desire. The domain of desire related to partner oriented feelings. SHBG was not independently associated with any assessment of sexual desire. No measure of serum testosterone or SHBG was independently associated with erectile function. The lack of association between serum testosterone levels and erectile dysfunction is somewhat surprising as it has been shown in men with ED, that serum free testosterone concentration correlates with impaired relaxation of cavernous endothelial and corporeal smooth muscle to vasoactive challenge, independent of age [283]. However, penile tissue possesses high concentrations of locally synthesised androgens and thus androgen-dependent functions need not reflect circulating androgen levels [284]. It is well documented in rats, that testosterone is required for adequate function of nitric oxide synthase, which produces nitric oxide necessary for relaxation of cavernosal endothelial and corporeal smooth muscle resulting in erection [285]. There is also possible non-nitric oxide dependent effects of testosterone on penile erection [286].

There is very little high-level evidence of an association between serum testosterone level and sexual desire in ageing men in the current literature, despite the wide-held belief. Schiavi et al. (1991) and Sadowsky et al. (1993) investigated the association of endogenous serum testosterone levels with sexual behaviour, including measures of desire [287, 288]. Schiavi et al. (1991) studied 77 healthy

married men between the ages of 45 and 74 years and demonstrated a strong decline in sexual desire with increasing age and an independent but lesser association with BT but not total T [287]. Sadowsky et al. (1993) demonstrated, cross-sectionally in 60 men aged 65 to 80 years, that age was the dominating factor in low levels of sexual desire and that there was no association with serum testosterone level independent of age or marital status [288]. Moreover, there was no significant difference in total testosterone levels between men with low, moderate and high levels of sexual desire in 180 men who attended a hospital-based ED clinic [289].

The present study demonstrates, perhaps for the first time, a convincing cross-sectional association between measures of serum testosterone and level of sexual desire after adjusting for inter-related socio-demographic variables, disease status and medication use. Many other independent associations with lower sexual desire (namely, marital status, income, lower alcohol intake, respiratory disease and use of urological medications) and poorer erectile function (income, hypertension, diabetes, OSA and use of urological and digestive medications) have also been demonstrated in this study, which highlights the multi-dimensional biological, psychological, pharmacological and sociological nature of sexual dysfunction. Krause et al. (2000) demonstrated that the risk of having reduced libido was lower in psychoneurological diseases and diabetes in 169 male patients presenting with sexual dysfunction and that testosterone levels were not associated with the risk of having reduced libido, penile rigidity, arousal or duration of erection, reduced morning erections or ability to masturbate [290].

The lack of association of sexual dysfunctions of desire and erectile function with abdominal obesity, as estimated by waist circumference was surprising. It appears that obesity related metabolic disorders such as diabetes and OSA are more likely to impact on sexual function than obesity per se . However, the lack of independent associations with obesity may be a function of prevalence bias in the current cohort. As shown in Chapter 4.0, the prevalence of obesity defined by both waist and BMI criteria was higher than reported by most other Australian and international studies, whereas the prevalence of

diabetes was 9%, reflective of the national prevalence. The high degree of overweight and obesity in the current cohort may have attenuated the ability to show significant associations with sexual dysfunction.

5.4 LOWER URINARY TRACT SYMPTOMS AND MAXIMAL URINARY FLOW RATE: RELATION TO AGE AND PLASMA TESTOSTERONE LEVELS.

SUMMARY

The prevalence of lower urinary tract symptoms (LUTS), benign prostatic hyperplasia (BPH) and reduced maximal urinary flow rates (Qmax) increase with ageing. Prostate growth and detrusor muscle contractility are effected by androgens. This chapter investigated the cross-sectional associations between serum testosterone (T) levels, LUTS and Qmax. Data were from the FAMAS as described in Chapter 4.0. In multiple regression models controlling for confounding variables, no measure of serum testosterone or SHBG was independently related to obstructive or irritative LUTS. The strongest, most consistent factor independently associated with higher obstructive and irritative LUTS scores was having an enlarged prostate. Older age and taking medication for conditions of the digestive system were independently associated with higher obstructive and irritative LUTS scores. In addition, not having a metabolic, endocrine or nutritional health condition was independently associated with higher obstructive LUTS and being hypertensive was independently associated with higher irritative LUTS scores. No measure of serum T or SHBG was independently associated with Qmax. Older age and higher free PSA were major factors independently associated with lower Qmax. This study shows that circulating T and SHBG levels do not independently contribute to the presence of LUTS and/or low Qmax in men as they age. Enlargement of the prostate and hypertension in older men and to a lesser degree taking medication for digestive disorders appear to be the major factors contributing to LUTS and higher serum free PSA levels are associated with lower Qmax. Both higher obstructive and irritative LUTS are associated with poorer erectile function, independent of age and other covariates.

INTRODUCTION

The prevalence of lower urinary tract symptoms (LUTS) such as urgency, frequency, nocturia, incontinence and reduced urine flow, increase with age [291, 292] and may significantly affect quality of life and sexual functioning. Benign prostatic hyperplasia (BPH) also increases with age, being present in as many as 50% of men aged 50, and in nearly 90% of autopsies in men age over 80 [293]. It is usually assumed that BPH is responsible for LUTS, particularly when the urine flow is reduced. However numerous cross sectional studies have shown either no, or inconsistent relationships between LUTS, BPH and urine flow [294, 295]. Moreover urine flow may be low in young men without symptoms. Concomitant detrusor instability [296] or other factors may predict LUTS in men with BPH. Specifically, it is expected that the longitudinal rate of change in maximal urine flow rate will correlate more strongly with symptom scores than the flow rate per se. In animals, T has been shown to inhibit detrusor muscle contraction [297] and therefore low T levels may promote unstable function of the detrusor muscle and LUTS, particularly in men with concomitant BPH. The prostate is androgen-dependent, in particular to DHT that is produced within the gland via 5α-reduction from T. The relative contribution of changes in androgens to LUTS is unclear. It is proposed that the age at which the first discernible fall in T levels occurs will have the most significant bearing on the age at which LUTS appear and the prostate begins to increase in size. In cross sectional studies, prostate volume is not significantly related to T, but increases with increasing age and body mass index (BMI) and decreases with increasing levels of SHBG [243]. Neither elevated T nor DHT predispose men to BPH [294].

Prostate specific antigen (PSA) is a glycoprotein produced by prostatic epithelium. Serum levels of PSA correlate positively with age. PSA “screening” for prostate cancer remains controversial with problems associated with sensitivity and specificity for prostate cancer. Recent reports suggest that a lower threshold level of PSA for recommending prostate biopsy may improve the clinical value of the PSA test

(Choong ref#1 from Florey) for prostate cancer. Not all microfoci of cancer within a gland progress to become clinically significant [298].

The previous chapter investigated and described the associations between erectile function, age and plasma testosterone levels. This chapter assesses and describes the association between obstructive and irritative LUTS, maximal urinary flow rate, age and plasma testosterone levels. The chapter concludes with an investigation of the inter-relations between LUTS and erectile function.

MATERIALS AND METHODS

PARTICIPANT SELECTION

Participants were male volunteers (N = 568), living in the North and West suburbs of Adelaide and recruited at random from the EWP's as described in Chapter 4.0.

MEASUREMENTS

All assessments were performed according to the methods described in Chapter 4.0. Specifically, obstructive and irritative LUTS were assessed using the IPSS (Barry et al. J Urol 1992). Urine flow rates and volumes were assessed by direct uroflowmetery using UROCAP-II as described in Chapter 4.0. Morning blood samples were obtained as described in Chapter 4.0 and total T, SHBG, total PSA and IGF-1 were measured as described in Chapter 2.0. BT was measured and cBT calculated as described in Chapter 3.0. Free PSA was measured as described in Chapter 4.0.

STATISTICAL ANALYSES

Stratified and probability weighted simple linear regression was performed to assess the associations of age and plasma T levels with obstructive and irritative LUTS and maximum urine flow rate. Multiple linear regression analysis, using the same strata and probability weighting was used to control for confounding in the associations of plasma T levels with LUTS and maximum urine flow rate. Regression coefficients and 95% confidence intervals (CI's) were reported. Post-estimation determination of linear combinations of factors was also performed to determine inter-relatedness of the effects on the outcome variable.

RESULTS

DEMOGRAPHICS

All men completed the IPSS. The mean obstructive and irritative LUTS scores by age group, school-leaving age, post-secondary qualifications, annual gross household income and work status, DSS pension, marital status and country of birth are shown in Appendix VII (Tables VII.I & VII.II respectively). Both obstructive and irritative LUTS increased with increasing age (Figure 5.4.1). In age-adjusted analyses, obstructive LUTS was not associated with any demographic variable. Greater irritative LUTS was associated with being widowed or never married (Table 5.4.1).

Three hundred and thirty eight men completed a successful maximum urinary flow rate test (i.e. voided at least 120 mL). Mean maximum urinary flow rates are shown by age group, school-leaving age, post-secondary qualifications, annual gross household income and work status, DSS pension, marital status and country of birth in Appendix VII (Table VII.III). Qmax declined with increasing age (Figure 5.4.1). In age-adjusted analyses, lower Qmax was associated with being widowed or never married (Table 5.4.1).

	Obstrcutive LUTS	
	Coeff (95% CI)	P
Age	0.057 (0.034 - 0.079)	< 0.0001
	Irritative LUTS	
Age	0.073 (0.046 - 0.099)	< 0.0001
Marital status	0.431 (0.055 - 0.806)	0.025
	Max urine flow rate	
Age	-0.271 (-0.35 - -0.19)	< 0.0001
Marital status	-1.269 (-2.309 - -0.229)	0.017

Table 5.4.1 Significant age-adjusted associations of demographics with obstructive and irritative LUTS, as measured by IPSS and maximum urine flow rate

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

RISK FACTORS AND BEHAVIOURS

In age-adjusted analyses, greater obstructive LUTS was associated with lower systolic blood pressure and BMI and greater irritative LUTS was associated with higher serum IGF-1 levels (Table 5.4.2). A higher Qmax was associated with lower total and free serum PSA and with greater physical activity level, independent of age (Table 5.4.2).

CHRONIC DISEASE, SURGICAL PROCEDURES AND MEDICATIONS

In age-adjusted analyses, greater obstructive LUTS was associated with anxiety, enlargement of the prostate, not having a metabolic, endocrine or nutritional health condition and taking medication for digestive, respiratory and genital health conditions (Table 5.4.3). Independent of age, greater irritative LUTS was associated with enlargement of the prostate, hypertension, a higher probability of OSA, not having a circulatory health condition and taking medication for digestive, circulatory, musculoskeletal, respiratory and genital health conditions (Table 5.4.3). Higher Qmax was associated with prostate removal, having a respiratory health condition, not having had bladder surgery, not having a neurological health condition and not taking medications for a urological condition, independent of age (Table 5.4.3).

	Obstrcutive LUTS	
	Coeff (95% CI)	P
Systolic blood pressure	-0.016 (-0.03 - -0.0007)	0.04
BMI	-0.058 (-0.11 - -0.005)	0.03
	Irritative LUTS	
IGF-1	0.03 (0.003 - 0.056)	0.027
	Max urine flow rate	
Total PSA	-0.021 (-0.03 - -0.01)	< 0.0001
Free PSA	-0.267 (-0.498 - -0.035)	0.024
Physical activity level	0.947 (0.028 - 1.867)	0.043

Table 5.4.2 Significant age-adjusted associations of chronic disease risk factors and behaviours with obstructive and irritative LUTS, as measured by IPSS and maximum urine flow rate

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

	Obstrcutive LUTS	
	Coeff (95% CI)	P
Anxiety	0.877 (0.094 - 1.66)	0.028
Enlarged prostate	2.644 (1.338 - 3.949)	< 0.0001
Health condition; metabolic, endocrine, nutritional	-1.128 (-1.718 - -0.538)	< 0.0001
Medication, digestive	1.053 (0.229 - 1.878)	0.012
Medication, respiratory	0.915 (0.127 - 1.704)	0.023
Medication, genital	1.682 (0.038 - 3.326)	0.045
	Irritative LUTS	
Enlarged prostate	2.20 (0.789 - 3.612)	0.002
High blood pressure	1.094 (0.396 - 1.792)	0.002
Probability of OSA	1.754 (0.517 - 2.991)	0.006
Health condition, circulatory	-1.042 (-1.86 - -0.224)	0.013
Medication, digestive	1.325 (0.374 - 2.275)	0.006
Medication, circulatory	0.706 (-0.001 - 1.413)	0.05
Medication, musculoskeletal	1.05 (0.116 - 1.991)	0.028
Medication, respiratory	1.027 (0.108 - 1.945)	0.029
Medication, genital	1.731 (0.049 - 3.414)	0.044
	Max urine flow rate	
Prostate removal	4.704 (2.085 - 7.325)	< 0.0001
Bladder surgery	-3.923 (-7.119 - -0.726)	0.016
Health condition, neurological	-5.207 (-9.46 - -0.955)	0.017
Health condition, respiratory	3.242 (0.24 - 6.245)	0.034
Medication, urological	-3.959 (-6.803 - -1.115)	0.007

Table 5.4.3 Significant age-adjusted associations of chronic disease, urogenital surgical procedures and medication use with obstructive and irritative LUTS, as measured by IPSS and maximum urine flow rate

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

SERUM TESTOSTERONE

In age-adjusted analyses, no measure of serum testosterone or SHBG was associated with obstructive or irritative LUTS or with Qmax.

MULTIVARIATE PREDICTIVE MODELS FOR LUTS AND QMAX

No measure of serum testosterone or SHBG was independently related to obstructive LUTS (Table 5.4.4). Older age, lower BMI and not having a metabolic, endocrine or nutritional health condition were independently associated with a higher obstructive LUTS scores (Table 5.4.4). In a predictive model, not including serum testosterone or SHBG, the major independent predictors of greater obstructive LUTS were older age, enlargement of the prostate, not having a metabolic, endocrine or nutritional health condition and taking medication for a digestive health condition (Table 5.4.5).

No measure of serum testosterone or SHBG was independently related to irritative LUTS (Table 5.4.6). The strongest factors independently associated with higher irritative LUTS scores were older age, being widowed or never married, hypertension, a higher probability of OSA, and taking medication for a genital health condition (Table 5.4.6). In a predictive model, not including serum testosterone or SHBG, the major independent predictors of greater irritative LUTS were older age, being widowed or never married, higher serum IGF-1, enlargement of the prostate, hypertension, higher probability of OSA, not having a circulatory health condition and taking medication for digestive and musculoskeletal health conditions (Table 5.4.7).

No measure of serum testosterone or SHBG was independently related to Qmax (Table 5.4.8). Older age, being widowed or never married, not having a respiratory health condition and taking medication for a urological health condition were independently associated with lower Qmax (Table 5.4.8). In a

predictive model, not including serum testosterone or SHBG, the major independent predictors of lower Qmax were older age, being widowed or never married, having a lower total and higher free PSA, not having had a prostate removal, not having a respiratory health condition and taking medication for a urological health condition (Table 5.4.9).

	Total T	
	Coeff (95% CI)	P
Total T	-0.015 (-0.057 - 0.027)	0.488
Age	0.063 (0.035 - 0.091)	< 0.0001
Systolic blood pressure	-0.01 (-0.026 - 0.005)	0.187
BMI	-0.05 (-0.106 - 0.007)	0.084
Health condition; metabolic, endocrine, nutritional	-0.916 (-1.551 - -0.281)	0.005
	BT	
BT	-0.041 (-0.107 - 0.025)	0.225
Age	0.053 (0.028 - 0.077)	< 0.0001
BMI	-0.06 (-0.112 - -0.008)	0.023
	cBT	
cBT	-0.006 (-0.085 - 0.072)	0.875
Age	0.056 (0.032 - 0.081)	< 0.0001
	FT	
FT	-0.001 (-0.002 - 0.001)	0.449
Age	0.054 (0.029 - 0.078)	< 0.0001
BMI	-0.062 (-0.113 - -0.01)	0.02
	SHBG	
SHBG	-0.006 (-0.022 - 0.01)	0.45

Age	0.053 (0.029 - 0.078)	< 0.0001
BMI	-0.055 (-0.109 - -0.001)	0.045
Health condition; metabolic, endocrine, nutritional	-0.902 (-1.507 - -0.297)	0.004
Medication, genital	1.611 (-0.036 - 3.257)	0.055

Table 5.4.4 Predictive models of serum testosterone and SHBG with obstructive LUTS, as measured by IPSS

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(5, 562) = 6.37$, $P < 0.0001$, $R2 = 0.092$. BT model: $F(3, 564) = 9.79$, $P < 0.0001$, $R2 = 0.086$. cBT model: $F(2, 565) = 13.0$, $P < 0.0001$, $R2 = 0.075$. FT model: $F(3, 564) = 9.44$, $P < 0.0001$, $R2 = 0.085$. SHBG model: $F(5, 562) = 6.65$, $P < 0.0001$, $R2 = 0.102$.

	Obstructive LUTS	
	Coeff (95% CI)	P
Age	0.036 (0.008 - 0.063)	0.011
Systolic blood pressure	-0.007 (-0.02 - 0.006)	0.294
BMI	-0.035 (-0.088 - 0.018)	0.195
Anxiety	0.666 (-0.058 - 1.391)	0.071
Enlarged prostate	2.307 (0.991 - 3.624)	0.001
Health condition; metabolic, endocrine, nutritional	-0.812 (-1.458 - -0.165)	0.014
Medication, digestive	0.792 (0.015 - 1.57)	0.045
Medication, respiratory	0.459 (-0.276 - 1.195)	0.22
Medication, genital	0.741 (-0.892 - 2.373)	0.373

Table 5.4.5 Predictive model of obstructive LUTS, as measured by IPSS

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: $F(9, 558) = 6.63$, $P < 0.0001$, $R2 = 0.187$.

	Total T	
	Coeff (95% CI)	P
Total T	0.023 (-0.02 - 0.067)	0.295
Age	0.058 (0.03 - 0.086)	< 0.0001
Marital status	0.368 (0.001 - 0.736)	0.049
Hypertension	0.996 (0.285 - 1.708)	0.006
Probability of OSA	1.408 (0.158 - 2.657)	0.027
	BT	
BT	-0.017 (-0.088 - 0.054)	0.643
Age	0.075 (0.048 - 0.124)	< 0.0001
Marital status	0.436 (0.06 - 0.812)	0.023
	cBT	
cBT	0.004 (-0.085 - 0.093)	0.932
Age	0.073 (0.045 - 0.101)	< 0.0001
	FT	
FT	0.0003 (-0.002 - 0.002)	0.745
Age	0.067 (0.037 - 0.097)	< 0.0001
Marital status	0.382(0.018 - 0.746)	0.04
Probability of OSA	1.636 (0.412 - 2.859)	0.009
	SHBG	

Age	0.054 (0.021 - 0.087)	< 0.0001
Probability of OSA	1.789 (0.54 - -3.039)	0.005
Medication, genital	1.741 (0.092 - 3.39)	0.039

Table 5.4.6 Predictive models of serum testosterone and SHBG with irritative LUTS, as measured by IPSS

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(5, 562) = 9.85$, $P < 0.0001$, $R2 = 0.124$. BT model: $F(3, 564) = 10.80$, $P < 0.0001$, $R2 = 0.094$. cBT model: $F(2, 565) = 14.41$, $P < 0.0001$, $R2 = 0.081$. FT model: $F(4, 563) = 11.04$, $P < 0.0001$, $R2 = 0.107$. SHBG model: $F(4, 563) = 12.59$, $P < 0.0001$, $R2 = 0.107$.

	Irritative LUTS	
	Coeff (95% CI)	P
Age	0.032 (0.003 - 0.062)	0.032
Marital status	0.417 (0.083 - 0.751)	0.015
Serum IGF-1	0.029 (0.004 - 0.054)	0.024
Enlarged prostate	2.147 (0.734 - 3.56)	0.003
Hypertension	0.803 (0.052 - 1.553)	0.036
Probability of OSA	1.226 (0.024 - 2.247)	0.046
Health condition, circulatory	-1.305 (-2.13 - -0.48)	0.002
Medication, digestive	1.016 (0.121 - 1.91)	0.026
Medication, circulatory	0.338 (-0.499 - 1.176)	0.428
Medication, musculoskeletal	0.848 (0.006 - 1.691)	0.048
Medication, respiratory	0.506 (-0.275 - 1.286)	0.204
Medication, genital	1.148 (-0.518 - 2.814)	0.176

Table 5.4.7 Predictive model of irritative LUTS, as measured by IPSS

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: $F(12, 551) = 6.51$, $P < 0.0001$, $R2 = 0.215$.

	Total T	
	Coeff (95% CI)	P
Total T	-0.045 (-0.167 - 0.077)	0.47
Age	-0.289 (-0.365 - -0.212)	< 0.0001
Marital status	-1.23 (-2.30 - -0.161)	0.024
Health condition, respiratory	3.434 (0.514 - 6.353)	0.021
	BT	
BT	-0.112 (-0.384 - 0.161)	0.42
Age	-0.295 (-0.374 - -0.216)	< 0.0001
Marital status	-1.266 (-2.329 - -0.202)	0.02
Medication, urological	-4.519 (-7.229 - -1.808)	0.001
	cBT	
cBT	0.022 (-0.386 - 0.431)	0.914
Age	-0.282 (-0.351 - -0.188)	< 0.0001
	FT	
FT	0.0005 (-0.007 - 0.008)	0.893
Age	-0.282 (-0.361 - -0.204)	< 0.0001
Marital status	-1.279 (-2.332 - -0.226)	0.017
	SHBG	
SHBG	-0.03 (-0.085 - 0.024)	0.277
Age	-0.261 (-0.343 - -0.18)	< 0.0001

Table 5.4.8 Predictive models of serum testosterone and SHBG with Qmax

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(4, 333) = 17.33$, $P < 0.0001$, $R2 = 0.18$. BT model: $F(4, 333) = 14.14$, $P < 0.0001$, $R2 = 0.175$. cBT model: $F(2, 335) = 22.79$, $P < 0.0001$, $R2 = 0.153$. FT model: $F(3, 334) = 17.62$, $P < 0.0001$, $R2 = 0.169$. SHBG model: $F(2, 335) = 23.24$, $P < 0.0001$, $R2 = 0.156$.

	Qmax	
	Coeff (95% CI)	P
Age	-0.279 (-0.361 - -0.197)	< 0.0001
Marital status	-1.157 (-2.138 - -0.176)	0.021
Serum total PSA	0.379 (0.119 - 0.639)	0.004
Serum free PSA	-3.456 (-5.751 - -1.16)	0.003
Physical activity level	0.818 (-0.068 - 1.704)	0.07
Prostate removal	5.452 (3.611 - 7.294)	< 0.0001
Bladder surgery	-2.025 (-4.911 - 0.861)	0.168
Health condition, neurological	-3.42 (-7.72 - 0.881)	0.119
Health condition, respiratory	3.818 (1.253 - 6.384)	0.004
Medication, urological	-3.721 (-6.374 - -1.067)	0.006

Table 5.4.9 Predictive model of Qmax

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: $F(10, 326) = 18.63$, $P < 0.0001$, $R2 = 0.22$.

ASSOCIATIONS BETWEEN LUTS, MAXIMAL URINARY FLOW RATE AND ERECTILE FUNCTION

Poorer erectile function, as determined by the IIEF, was significantly associated with both greater obstructive and irritative LUTS independent of age, marital status, and digestive medication use (Table 5.4.10). Erectile function was not associated with maximal urinary flow rate independent of age, marital status and urological medications.

	Obstructive LUTS	
	Coeff (95% CI)	P
IIEF_EF	-0.045 (-0.075 - -0.015)	0.003
Age	0.033 (0.01 - 0.056)	0.005
Medication, digestive	1.015 (0.201 - 1.828)	0.015
	Irritative LUTS	
IIEF_EF	-0.042 (-0.081 - -0.003)	0.036
Age	0.05 (0.023 - 0.077)	< 0.0001
Marital status	0.349 (-0.025 - 0.723)	0.067
Medication, urological	1.327 (0.385 - 2.269)	0.006

Table 5.4.10 Independent associations of erectile function with obstructive and irritative LUTS

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Obstructive LUTS model: $F(3, 556) = 11.82$, $P < 0.0001$, $R2 = 0.11$. Irritative LUTS model: $F(4, 5556) = 9.53$, $P < 0.0001$, $R2 = 0.12$.

DISCUSSION

This chapter describes the association with obstructive and irritative LUTS and maximum urine flow rate of the various measures of serum testosterone and SHBG. This work aimed to determine if circulating testosterone levels contribute to the presence of LUTS and/or low maximum urinary flow rate.

Serum testosterone and SHBG were not independently associated with either obstructive or irritative lower urinary tract symptoms or with maximum urine flow rates. Inverse associations between the free and bioavailable estimates of testosterone and both obstructive and irritative LUTS were observed, but these associations were confounded by age, marital status and BMI. After controlling for these effects the association with free and bioavailable testosterone levels lost significance. Similarly, a positive association between SHBG levels and obstructive and irritative LUTS was confounded by age, OSA, BMI, metabolic, endocrine or nutritional conditions and genital medications. SHBG was also inversely associated with maximum urine flow, in a relationship that was confounded only by age. Supportive of the current data, Haidinger et al. (2000) reported, in a cross-sectional study, that age was the single most influential predictor of LUTS, as measured by the IPSS, in 1557 Viennese men aged 40 – 96 years [292]. This study however, did not measure serum testosterone or SHBG levels and men aged less than 40 years were excluded from analysis, along with men who had a history of prostate surgery or were taking medication for the treatment of LUTS.

In the present study, enlargement of the prostate was the dominant risk factor for both obstructive and irritative LUTS. Interestingly, lower total PSA and higher free PSA were associated with lower maximal urine flow rate in the current cohort. Meigs et al. (2001) reported that elevated free PSA levels predicted benign

prostatic hyperplasia, independent of total PSA levels in 1019 men without prostate cancer at 9 year follow-up, from the Massachusetts Male Aging Study cohort [298]. Men who had prostatectomy had higher maximal urine flow rates but surprisingly, TURP was not associated with higher maximal urine flow rate in the current cohort; men who took urological medications had poorer maximal urine flow.

It appears from the present data that use of digestive medications may impact the lower urinary tract, increasing both obstructive and irritative symptoms. These data are, however, cross-sectional and it is difficult to assign effect to this association. Nevertheless, there was no statistical association between LUTS and digestive health conditions, which would be expected if LUTS was the cause of digestive medication use. There is a lack of literature on the effects of digestive system medications on the lower urinary tract.

Finally, obstructive and irritative LUTS appear to be independently associated with poorer erectile function. Similar age and co-morbidity independent associations have been shown in two large multi-national studies with centres in the USA, Europe and Korea [282, 299].

In conclusion, it appears that ageing, prostate enlargement and concomitant disease and medication use impact significantly on the severity of both obstructive and irritative LUTS. There is no direct association between any measure of serum testosterone or SHBG and LUTS or maximal urine flow rate. Higher levels of free PSA, indicating prostate enlargement are highly predictive of lower maximal urine flow rates. Of great clinical importance is the independent association between LUTS and ED. Both conditions can have profound but variable levels of bothersomeness in ageing men and it has been estimated that over 60% of Australian men bothered by LUTS do not seek medical help [291]. These co-existing conditions raise interesting management issues and it is recommended that older men presenting with one condition also be investigated for the other.

5.5 THE ASSOCIATIONS OF TOTAL, BIOAVAILABLE AND FREE TESTOSTERONE AND SHBG WITH NEUROPSYCHOLOGICAL FUNCTION AND MOOD.

SUMMARY

This chapter reports cross-sectional associations of serum testosterone and SHBG levels with various clinical measures of neuropsychological function including visuospatial function, memory and mood. Data were from the FAMAS as described in Chapter 4.0. Serum testosterone and SHBG levels were not associated with any of the measures of neuropsychological function performed in this study. There was a definite trend towards an association between lower serum levels of bioavailable testosterone and greater levels of depression, independent of potential confounders. Major predictors of higher depression scores in the present study were having anxiety, asthma and insomnia. Higher fasting serum triglycerides were associated with poorer executive function and with higher depression scores. Moreover, having diabetes and/or higher HbA1c levels was associated with slower finger tapping and higher depression scores. The major associations with aspects of poorer were lower physical activity, insomnia and depression, whilst osteoarthritis, neurological health conditions and taking urological medications were associated with better memory performance. Taken together, these data indicate that diabetes and hypertriglyceridemia are independently associated with poorer cognitive outcomes. Androgens (possibly through conversion to oestradiol) may influence cognitive function through improved glycaemic control or effects on serum triglycerides and leptin at the blood-brain-barrier. Mood may be associated independently with BT levels and the present study shows a positive trend towards this association. The presence of anxiety, asthma and

insomnia as well as diabetes and hypertriglyceridemia were also major factors in higher depression scores. Demographic factors such as age, income, education and pension status variably modified associations with some neuropsychological functions.

INTRODUCTION

Positive relationships between serum testosterone (T) levels and mood and wellbeing have been reported [50, 83]. Hypogonadal men may be more depressed, angered, fatigued and confused than infertile, treated eugonadal or normal men [82]. BT has been reported to be 17% lower in categorically defined depressives than in healthy men [50]. The cause and effect relationships between changes in measures of T and emotional health and the interactions with social, demographic and lifestyle factors remain unknown. Total T and BT have an effect on visuospatial ability, but the relationship is quadratic (U-shaped) [84, 85], suggesting that impairment occurs when T levels are too high or too low. Increasing age is associated with declines in cognitive function. There are significant individual differences in age related cognitive changes; the factors responsible for these are poorly characterized. In the Baltimore Longitudinal Study of Aging, total T levels did not relate to any measure of cognitive function, but a higher calculated free testosterone was associated with better baseline scores on visual and verbal memory and a slower decline in visual memory [300]. These data emphasize that (i) it is important to identify the best measure of T status, (ii) relationships need to be studied in a longitudinal rather than purely cross-sectional manner and (iii) interaction with other factors must be accounted for.

This chapter reports the cross-sectional associations of serum testosterone and SHBG levels with various clinical measures of neuropsychological function including visuospatial function, memory and mood. Data come from the Florey Adelaide Ageing Male Study.

MATERIALS AND METHODS

PARTICIPANT SELECTION

Participants were male volunteers (N = 568), living in the North and West suburbs of Adelaide and recruited at random from the Electronic White Pages as described in Chapter 4.0.

MEASUREMENTS

All assessments were performed according to the methods described in Chapter 4.0. Specifically, morning blood samples were obtained and assayed for total T and SHBG and FT was calculated as described in Chapter 4.0. BT was measured and cBT calculated as described in Chapter 3.0. Neuropsychological assessments; trail making tests, Fuld object memory evaluation, finger tapping tests and the Beck Depression inventory (BDI) were conducted as described in Chapter 4.0. The trail making tests are reported as the ratio of TMT-B:TMT-A, an index of executive function, lower scores indicate better executive function. The Fuld object memory test is reported as repeated object retrievals and ineffective object reminders (difference between first immediate and final delayed trials). Higher repeated object retrievals indicate improvement in object recall from first to last trial. Lower ineffective object reminders indicate improvement in recalling objects previously forgotten from first to last trial. Only the dominant hand finger tapping scores are reported in this Chapter. Cigarette smoking, physical activity level and alcohol intake and the daily dietary intake of energy, fat, carbohydrate and protein were assessed by questionnaire as described in Chapter 4.0. Chronic disease included but was not limited to depression, diabetes, hypertension, hypercholesterolaemia, enlarged prostate and prostate cancer and current medications were determined by

self-report. History of surgical procedures including prostatectomy, trans-urethral resection of prostate (TURP) and other urogenital surgery was obtained by questionnaire as described in Chapter 4.0.

STATISTICAL ANALYSIS

Initially, bivariate associations with serum testosterone and SHBG levels were investigated. For categorical data including demographics, chronic disease, urogenital surgery and medication use, mean serum testosterone and SHBG concentrations were compared using a Wald test of significance. In these cases, data presented are means ± S.E. with associated 95% confidence intervals and comparative F and P statistics. Associations between continuous variables including SBP, waist circumference, cholesterol levels and other risk factor data, were determined by simple linear regression analysis, where data are presented as regression coefficients and associated 95% confidence intervals and R^2 and P statistics.

All associations were then adjusted for age using linear regression with age as a continuous variable.

Multiple linear regression analysis was used to account for confounding variables, considered to be variables that related to both the measure of plasma T of interest and the outcome variable at a level of $P < 0.05$. For multiple linear regression analysis the regression coefficient and 95% confidence intervals (CI's) are reported. All analyses were performed on stratified and probability weighted data as described in Chapter 4.0.

RESULTS

Three hundred and ninety-one men successfully completed all items on the BDI so that a total score could be calculated. Using the criteria of Beck et al. (1987) [184] (see Chapter 4.0, Table 4.1), 7% (N = 41) of men were mildly depressed, 3% (N = 17) were mild to moderately depressed and less than 1% (N = 4) was moderately to severely depressed. No men were classified as having severe depression based on these criteria.

DEMOGRAPHICS

Mean finger tapping on the dominant hand was significantly and inversely associated with increasing age (Figure 5.5.1 top panel). The TMT-B:TMT-A ratio was significantly and positively associated with increasing age (Figure 5.5.1 bottom panel). Repeated object retrieval and ineffective reminder memory variables and BDI scores were not significantly associated with age. Age-adjusted associations between demographics and dominant hand finger tapping, repeated retrieval and ineffective reminders from the first to the last memory trial, the TMT-B:TMT-A ratio and BDI scores are shown in Table 5.5.1. Faster dominant hand finger tapping was associated with older school leaving age, higher post school qualifications and gross annual household income, independent of age. There were no age-independent demographic associations with repeated object retrieval. Fewer ineffective object reminders were associated with lower household income independent of age. Greater BDI scores were associated with being retired and receiving a DSS pension independent of age.

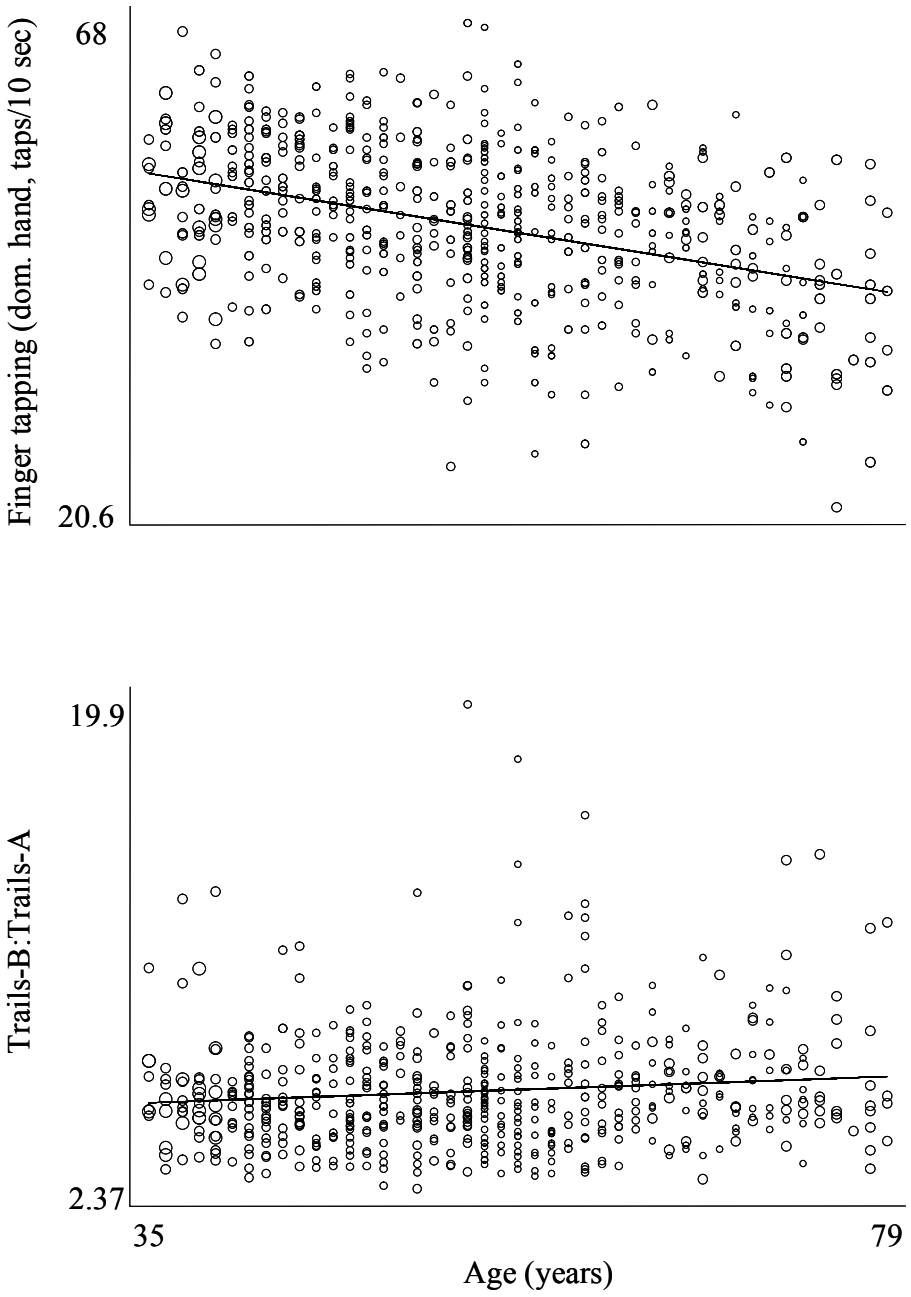

Figure 5.5.1 Associations of dominant hand finger tapping (top panel) and TMT-B:TMT-A ratio (bottom panel) with age

in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Size of data points is proportional to their weighting. Top panel: Coeff. = -0.263, $P < 0.0001$, $R^2 = 0.18$. Bottom panel: Coeff. = 0.021, $P = 0.014$, $R^2 = 0.016$.

	Finger tapping (dominant hand)	
	Coeff (95% CI)	P
Age	-0.263 (-0.319 - -0.208)	< 0.0001
School leaving age	0.669 (0.177 - 1.16)	0.008
Highest post school qualification	1.61 (0.561 - 2.66)	0.003
Gross annual household income	0.676 (0.169 - 1.18)	0.009
	Memory (Repeated object retrieval)	
No age independent associations		
	Memory (Ineffective object reminders)	
Gross annual household income	0.126 (0.043 - 0.209)	0.003
	TMT-B:TMT-A	
Age	0.021 (0.004 - 0.038)	0.014
School leaving age	-0.229 (-0.40 - -0.061)	0.008
	BDI	
Work status	1.94 (0.834 - 3.05)	0.001
DSS pension	-2.38 (-4.01 - -0.743)	0.004

Table 5.5.1 Significant age-adjusted associations of dominant hand finger tapping, repeated object retrieval, ineffective object reminders, TMT-B:TMT-A ratio and BDI score with demographic variables

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

CHRONIC DISEASE RISK FACTORS AND BEHAVIOURS

The significant age-adjusted associations of dominant hand finger tapping, repeated object retrieval and ineffective object reminders from the first to the last memory trial, the TMT-B:TMT-A ratio and BDI scores with chronic disease risk factors and lifestyle behaviours are shown in Table 5.5.2. Independent of age, faster finger tapping on the dominant had was associated with higher diastolic blood pressure, waist circumference and BMI, lower HbA1c and being a non-smoker. There was an age-independent trend towards better object retrieval with higher physical activity levels, but there were no age-independent risk factor/behaviour associations with ineffective object reminders. Poorer TMT-B:TMT-A ratios and BDI scores were both associated with higher fasting serum triglyceride levels, independent of age. Additionally, poorer BDI scores were associated with higher fasting serum insulin levels.

	Finger tapping (dominant hand)	
	Coeff (95% CI)	P
Diastolic blood pressure	0.083 (0.015 - 0.152)	0.018
Waist circumference	0.058 (0.007 - 0.109)	0.025
BMI	0.195 (0.062 - 0.328)	0.004
HbA1c	-1.11 (-1.77 - -0.452)	0.001
Cigarette smoking	1.68 (0.308 - 3.05)	0.016
	Memory (Repeated object retrieval)	
Physical activity level	0.146 (0.00005 - 0.291)	0.05
	Memory (Ineffective object reminders)	
No age-independent associations		
	TMT-B:TMT-A	
Fasting serum triglycerides	0.199 (0.049 - 0.348)	0.009
	BDI	
Fasting serum triglycerides	0.81 (0.123 - 1.50)	0.021
Fasting serum insulin	0.09 (0.031 - 0.148)	0.003

Table 5.5.2 Significant age-adjusted associations of dominant hand finger tapping, repeated object retrieval, ineffective object reminders, TMT-B:TMT-A ratio and BDI score with chronic disease risk factors and behaviours

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

CHRONIC DISEASE, SURGICAL PROCEDURES AND MEDICATIONS

Age-adjusted associations of dominant hand finger tapping, repeated object retrieval and ineffective object reminders from the first to the last memory trial, the TMT-B:TMT-A ratio and BDI scores with chronic disease, surgical procedures and medication use are shown in Table 5.5.3. Independent of age, slower finger tapping on the dominant hand was associated with diabetes, bladder surgery and taking medication for circulatory; metabolic, endocrine or nutritional; and urological health conditions. Poorer object retrieval was associated, independent of age, with anxiety, depression and insomnia. Hypercholesterolaemia, osteoarthritis and taking urological medications was associated with better object retrieval scores independent of age. Poorer ability to remember items after being reminded of them was associated with depression; having prostate cancer and taking neurological medications was associated with better ability on this function, independent of age. Taking urological medications was associated with better TMT-B:TMT-A ratios independent of age. Greater BDI scores were associated with multiple chronic diseases and medications.

	Finger tapping (dominant hand)	
	Coeff (95% CI)	P
Diabetes	-3.67 (-5.90 - -1.44)	0.001
Bladder surgery	-6.94 (-11.39 - -2.49)	0.002
Medication, circulatory	-1.82 (-3.33 - -0.30)	0.019
Medication; Met. Endo. Nut.	-1.68 (-3.33 - -0.028)	0.046
Medication, urological	-5.83 (-11.61 - -0.056)	0.048
	Memory (Repeated object retrieval)	
Anxiety	-0.563 (-0.995 - -0.131)	0.011
Depression	-0.432 (-0.814 - -0.05)	0.027
Hypercholesterolaemia	0.318 (0.016 - 0.619)	0.039
Insomnia	-0.499 (-0.961 - -0.038)	0.034
Osteoarthritis	0.612 (0.142 - 1.08)	0.011
Medication, urological	1.68 (0.784 - 2.57)	< 0.0001
	Memory (Ineffective object reminders)	
Depression	0.306 (0.007 - 0.605)	0.045
Prostate cancer	-0.806 (-1.48 - -0.132)	0.019
Health condition, neurological	-0.874 (-1.68 - -0.067)	0.034
	TMT-B:TMT-A	
Medication, urological	-1.05 (-2.0 - -0.095)	0.031

	BDI	
Anxiety	4.91 (2.45 - 7.36)	< 0.0001
Asthma	2.71 (0.227 - 5.20)	0.033
Depression	5.94 (3.87 - 8.01)	< 0.0001
Diabetes	2.65 (0.209 - 5.10)	0.033
Insomnia	4.79 (2.53 - 7.06)	< 0.0001
Probability of OSA	3.62 (0.987 - 6.26)	0.007
Health condition, psychological	6.28 (0.266 - 12.29)	0.041
Medication, digestive	2.02 (0.399 -3.64)	0.015
Medication, circulatory	1.90 (0.282 - 3.52)	0.021
Medication, psychological	2.87 (0.977 - 4.75)	0.003
Medication; Met. Endo. Nut.	1.94 (0.255 - 3.63)	0.024
Medication, urological	4.35 (1.72 - 6.99)	0.001

Table 5.5.3 Significant age-adjusted associations of dominant hand finger tapping, repeated object retrieval, ineffective object reminders, TMT-B:TMT-A ratio and BDI score with chronic disease, urogenital surgery and medication use

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0.

SERUM TESTOSTERONE

Finger tapping, dominant hand

In age-adjusted analyses, no measure of serum testosterone or SHBG was associated with finger tapping speed on the dominant hand.

Repeated object retrieval and ineffective object reminders

In age-adjusted analyses, no measure of serum testosterone or SHBG was associated with repeated object retrieval, but higher levels of measured and calculated BT were associated with greater ineffective reminders from the initial to the delayed recall trial (Figure 5.5.2).

TMT-B:TMT-A ratio

In age-adjusted analyses, no measures of serum testosterone or SHBG was associated with the TMT-B:TMT-A ratio.

BDI score

In age-adjusted analyses, serum BT (Figure 5.2.3), but no other measure of serum testosterone or SHBG, was inversely associated with BDI score.

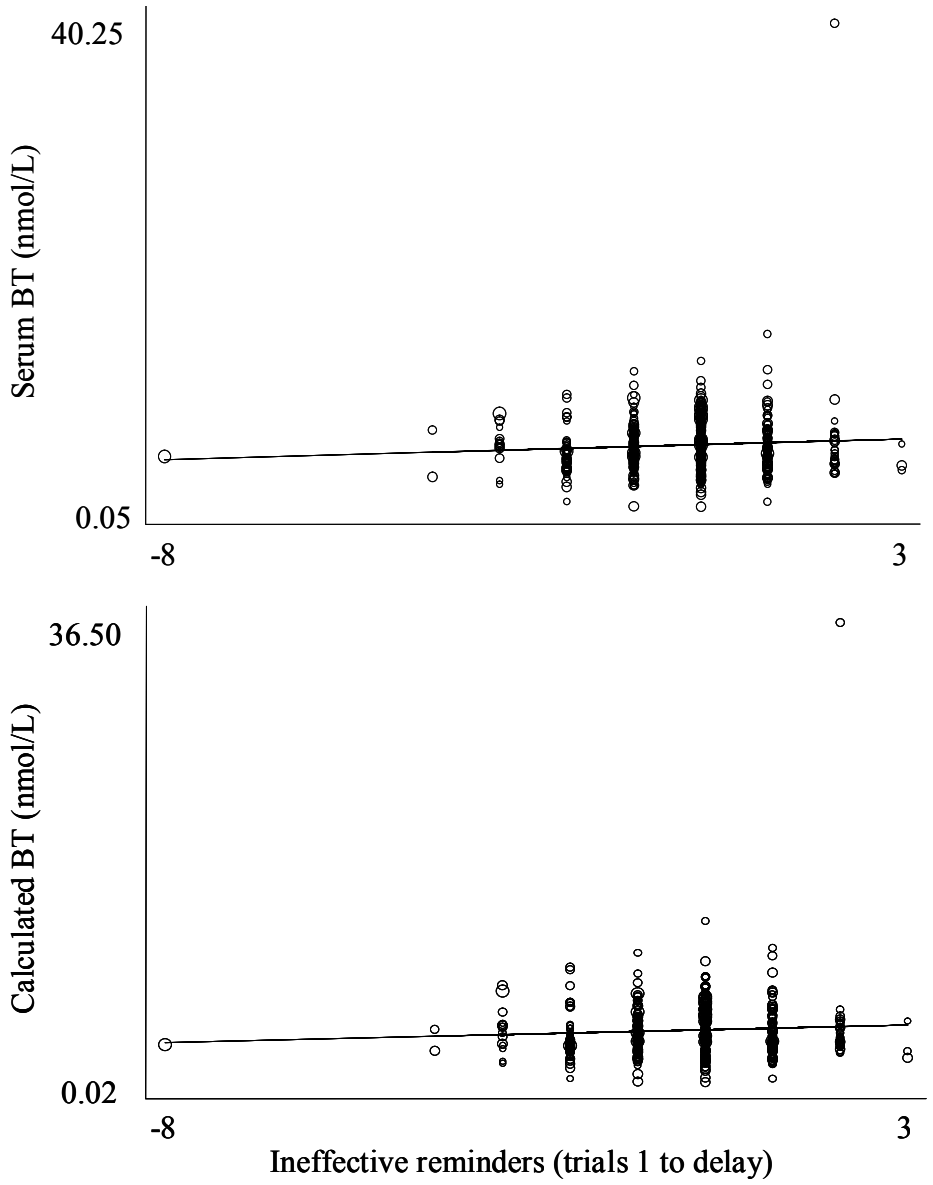

Figure 5.5.2 Associations of measured (top panel) and calculated (bottom panel) bioavailable testosterone with the difference in the number of ineffective object reminders between the first and the delayed recall trials of the Fuld object memory evaluation.

Data are from 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Size of data points is proportional to their weighting. Top panel: F(2, 563) = 4.06, Coeff. = 0.055, P = 0.005. Bottom panel: F(2, 563) = 2.65, Coeff. = 0.055, P = 0.022.

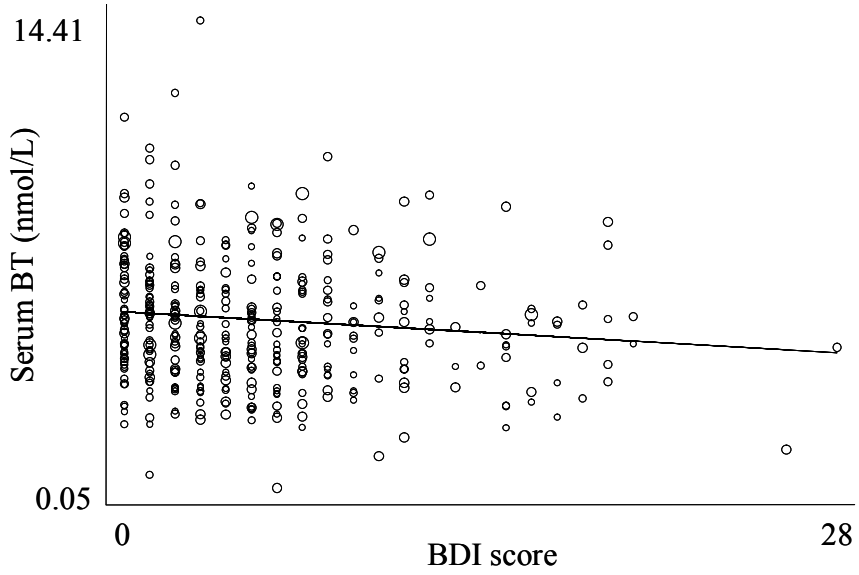

Figure 5.5.3 Associations of measured bioavailable testosterone with Beck depression inventory (BDI) score

in 568 men aged 35 – 80 years, recruited from random households in the North-west suburbs of Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Size of data points is proportional to their weighting. F(2, 388) = 2.30, Coeff. = -0.31, P = 0.047.

MULTIVARIATE PREDICTIVE MODELS FOR FINGER TAPPING, MEMORY, TRAIL MAKING AND DEPRESSION SCORES

Finger tapping

All testosterone and SHBG models predicted 21 – 23% of the heterogeneity in finger tapping scores on the dominant hand (Table 5.5.4). However, no measure of serum testosterone or SHBG was associated with finger tapping independent of covariates. The major independent predictors of slower finger tapping were older age, lower income, higher HbA1c and diabetes, cigarette smoking, smaller waist circumference and taking medications for metabolic, endocrine or nutritional health conditions (Table 5.5.4). In a predictive model, not including serum testosterone or SHBG, the major independent predictors of slower finger tapping were older age, younger school leaving age, lower post-school qualifications, higher HbA1c and a history of bladder surgery (Table 5.5.5).

Memory: repeated object retrieval and ineffective reminders

The BT model significantly predicted only 1% of the heterogeneity in repeated object retrieval scores on the Fuld object memory evaluation (Table 5.5.6). However, BT was not independently associated with repeated retrieval scores. The total T and SHBG models did not significantly predict repeated retrieval scores. Not models were established for cBT or FT as no confounding variables were identified. In a predictive model not including serum testosterone or SHBG levels, the major independent predictors of poorer repeated retrieval scores were being sedentary and having insomnia. Having osteoarthritis and taking urological medications was associated with better repeated retrieval scores independent of covariates (Table 5.5.7).

The total T model significantly predicted only 1% of the heterogeneity in ineffective reminder scores on the Fuld object memory evaluation (Table 5.5.8). However, total T was not independently associated with ineffective reminder scores. The cBT and SHBG models did not significantly predict ineffective reminder scores. No models were established for BT or FT as no confounding variables were identified. In a predictive model including all age-independent predictors of ineffective reminder scores, the major independent predictor of poorer scores was depression. Having a neurological health condition was independently associated with better ineffective reminder scores (Table 5.5.9).

	Total T	
	Coeff (95% CI)	P
Serum total T	-0.01 (-0.115 - 0.094)	0.884
Age	-0.223 (-0.285 - -0.161)	< 0.0001
Gross annual household income	0.481 (-0.009 - 0.97)	0.054
Diastolic blood pressure	0.044 (-0.025 - 0.114)	0.211
Waist circumference	-0.0006 (-0.121 - 0.12)	0.992
BMI	0.177 (-0.141 - 0.495)	0.275
HbA1c	-0.833 (-1.65 - -0.018)	0.045
Cigarette smoking	1.38 (0.048 - 2.70)	0.042
Diabetes	-2.64 (-5.25 - -0.033)	0.047
	BT	
Serum BT	-0.017 (-0.21 - 0.177)	0.866
Age	-0.245 (-0.301 - -0.190)	< 0.0001
Waist circumference	0.003 (-0.117 - 0.123)	0.964
BMI	0.224 (-0.085 - 0.533)	0.115
HbA1c	-0.925 (-1.74 - -0.109)	0.026
Cigarette smoking	1.62 (0.307 - 2.94)	0.016
Diabetes	-2.28 (-4.94 - 0.389)	0.094
Medication, urological	-4.99 (-10.45 - 0.472)	0.073
	cBT	
cBT	-0.017 (-0.223 - 0.189)	0.874
Age	-0.253 (-0.307 - -0.198)	< 0.0001
Waist circumference	0.079 (0.027 - 0.131)	0.003
HbA1c	-0.943 (-1.77 - -0.114)	0.026
Cigarette smoking	1.62 (0.317 - 2.93)	0.015

	FT	
FT	-0.002 (-0.006 - 0.003)	0.495
Age	-0.246 (-0.302 - -0.19)	< 0.0001
Waist circumference	-0.003 (-0.124 - 0.118)	0.963
BMI	0.239 (-0.074 - 0.552)	0.134
HbA1c	-0.975 (-1.81 - -0.145)	0.021
Cigarette smoking	1.51 (0.198 - 2.83)	0.024
Diabetes	-2.38 (-5.05 - 0.296)	0.081
	SHBG	
SHBG	0.014 (-0.028 - 0.056)	0.52
Age	-0.216 (-0.285 - -0.148)	< 0.0001
Gross annual household income	0.594 (0.087 - 1.10)	0.022
Diastolic blood pressure	0.058 (-0.012 - 0.128)	0.104
Waist circumference	-0.028 (-0.146 - 0.091)	0.645
BMI	0.225 (-0.093 - 0.544)	0.166
Medication; Met. Endo. Nut.	-1.90 (-3.54 - -0.256)	0.024

Table 5.5.4 Predictive models of serum testosterone and SHBG with finger tapping on the dominant hand

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(9, 549) = 16.80$, $P < 0.0001$, $R2 = 0.23$. BT model: $F(8, 555) = 18.19$, $P < 0.0001$, $R2 = 0.23$. cBT model: $F(6, 557) = 22.93$, $P < 0.0001$, $R2 = 0.22$. FT model: $F(7, 556) = 20.35$, $P < 0.0001$, $R2 = 0.22$. SHBG model: $F(7, 551) = 17.88$, $P < 0.0001$, $R2 = 0.21$.

	Finger tapping (dominant hand)	
	Coeff (95% CI)	P
Age	-0.184 (-0.251 - -0.118)	< 0.0001
School leaving age	0.267 (0.026 - 0.505)	0.03
Highest post-school qualification	1.31 (0.277 - 2.34)	0.013
Gross annual household income	0.237 (-0.261 - 0.736)	0.35
Diastolic blood pressure	0.051 (-0.019 - 0.122)	0.153
Waist circumference	0.007 (-0.11 - 0.124)	0.905
BMI	0.176 (-0.133 - 0.485)	0.263
HbA1c	-0.81 (-1.57 - -0.047)	0.037
Cigarette smoking	1.20 (-0.111 - 2.52)	0.073
Diabetes	-2.05 (-4.71 - 0.601)	0.129
Bladder surgery	-5.40 (-9.90 - -0.89)	0.019
Medication, circulatory	-1.49 (-2.99 - 0.005)	0.051
Medication; Met. Endo. Nut.	-0.10 (-1.82 - 1.62)	0.909
Medication, urological	-4.38 (-8.92 - 0.163)	0.059

Table 5.5.5 Predictive model of finger tapping on the dominant hand

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: $F(14, 540) = 12.93$, $P < 0.0001$, $R2 = 0.27$.

	Total T	
	Coeff (95% CI)	P
Serum total T	-0.005 (-0.027 - 0.017)	0.671
Hypercholesterolaemia	0.261 (-0.039 - 0.562)	0.088
	BT	
Serum BT	-0.011 (-0.054 - 0.031)	0.602
Medication, urological	1.69 (0.782 - 2.60)	< 0.0001
	SHBG	
SHBG	-0.002 (-0.011 - 0.008)	0.754
Hypercholesterolaemia	0.264 (-0.036 - 0.565)	0.085

Table 5.5.6 Predictive models of serum testosterone and SHBG with repeated object retrieval (trials 1 to delay), as measured by the Fuld object memory evaluation

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: F(2, 563) = 1.64, P = 0.19, R2 = 0.007. BT model: F(2, 563) = 6.84, P = 0.001, R2 = 0.01. SHBG model: F(2, 563) = 1.62, P = 0.20, R2 = 0.007.

	Memory (repeated object retriaval)	
	Coeff (95% CI)	P
Physical activity level	0.152 (0.01 - 0.294)	0.036
Anxiety	-0.33 (-0.913 - 0.254)	0.267
Depression	-0.143 (-0.638 - 0.352)	0.571
Hypercholesterolaemia	0.257 (-0.033 - 0.547)	0.082
Insomnia	-0.51 (-1.01 - -0.007)	0.047
Osteoarthritis	0.51 (0.067 - 0.954)	0.024
Medication, urological	1.53 (0.582 - 2.47)	0.002

Table 5.5.7 Predictive model of repeated object retrieval (trials 1 to delay), as measured by the Fuld object memory evaluation

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: $F(7, 558) = 5.45$, $P < 0.0001$, $R2 = 0.05$.

	Total T	
	Coeff (95% CI)	P
Serum total T	0.008 (-0.011 - 0.028)	0.389
Gross annual household income	0.089 (0.004 - 0.173)	0.04
	cBT	
cBT	0.031 (-0.017 - 0.079)	0.201
Prostate cancer	-0.588 (-1.25 - 0.073)	0.081
	SHBG	
SHBG	0.00006 (-0.007 - 0.007)	0.988
Gross annual household income	0.089 (0.004 - 0.173)	0.039

Table 5.5.8 Predictive models of serum testosterone and SHBG with ineffective object reminders (trials 1 to delay), as measured by the Fuld object memory evaluation

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: F(2, 558) = 3.17, P = 0.043, R2 = 0.01. cBT model: F(2, 563) = 2.96, P = 0.052, R2 = 0.009. SHBG model: F(2, 558) = 2.14, P = 0.12, R2 = 0.009.

	Memory (ineffective reminders)	
	Coeff (95% CI)	P
Serum BT	0.021 (-0.02 - 0.061)	0.322
Gross annual household income	0.08 (-0.009 - 0.169)	0.079
Depression	0.34 (0.048 - 0.631)	0.022
Prostate cancer	-0.526 (-1.17 - 0.121)	0.111
Health condition, neurological	-0.837 (-1.65 - -0.028)	0.043

Table 5.5.9 Predictive model of ineffective object reminders (trials 1 to delay), as measured by the Fuld object memory evaluation

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: F(5, 555) = 3.82, P = 0.002, R2 = 0.04.

Trail making test (TMT-B:TMT-A)

All testosterone and SHBG models predicted 2 – 3% of the heterogeneity in TMT-B:TMT-A ratios (Table 5.5.10). However, no measure of serum testosterone or SHBG was associated with TMT-B:TMT-A ratios independent of covariates. The major independent predictors of poorer TMT-B:TMT-A ratios were older age, higher fasting serum triglyceride levels. Taking urological medication was independently associated with better TMT-B:TMT-A ratios (Table 5.5.10). In a predictive model, not including serum testosterone or SHBG, the major independent predictors of poorer TMT-B:TMT-A ratios were older age and higher fasting serum triglyceride levels (Table 5.5.11).

BDI score

All testosterone, except cBT, and SHBG models significantly predicted 3 – 10% of the heterogeneity on BDI scores (Table 5.5.12). However, no measure of testosterone or SHBG was independently associated with BDI scores. The major independent predictors of poorer BDI scores were receiving a DSS pension, diabetes and higher fasting serum triglyceride levels. In a predictive model including all age-independent predictors of poorer BDI scores, the major independent predictors were anxiety, asthma and insomnia.

	Total T	
	Coeff (95% CI)	P
Serum total T	-0.0003 (-0.028 - 0.027)	0.984
Age	0.022 (0.005 - 0.039)	0.013
Fasting serum triglycerides	0.198 (0.047 - 0.349)	0.01
	BT	
Serum BT	0.004 (-0.073 - 0.074)	0.992
Age	0.021 (0.003 - 0.039)	0.023
Medication, urological	-1.04 (-2.00 - -0.093)	0.032
	FT	
FT	-0.005 (-0.002 - 0.001)	0.508
Age	0.02 (0.0009 - 0.038)	0.04
Fasting serum triglycerides	0.194 (0.047 - 0.341)	0.01
	SHBG	
SHBG	0.006 (-0.009 - 0.022)	0.403
Age	0.019 (-0.00001 - 0.038)	0.05
Fasting serum triglycerides	0.218 (0.053 - 0.383)	0.01

Table 5.5.10 Predictive models of serum testosterone and SHBG with TMT-B:TMT-A ratio

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: $F(3, 557) = 3.78$, $P = 0.01$, $R2 = 0.03$. BT model: $F(3, 559) = 3.81$, $P = 0.01$, $R2 = 0.02$. FT model : $F(3, 557) = 3.84$, $P < 0.01$, $R2 = 0.03$. SHBG model: $F(3, 557) = 3.97$, $P = 0.008$, $R2 = 0.03$.

	TMT-B:TMT-A ratio	
	Coeff (95% CI)	P
Age	0.019 (0.001 - 0.037)	0.037
School leaving age	-0.091 (-0.195 - 0.013)	0.085
Fasting serum triglycerides	0.196 (0.046 - 0.346)	0.011
Medication, urological	-0.722 (-1.53 - 0.083)	0.079

Table 5.5.11 Predictive model of TMT-B:TMT-A ratio

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Model: $F(4, 551) = 6.47$, $P < 0.0001$, $R2 = 0.05$.

	Total T	
	Coeff (95% CI)	P
Serum total T	-0.02 (-0.12 - 0.08)	0.698
DSS pension	-1.74 (-2.97 - -0.505)	0.006
Fasting serum triglycerides	0.676 (-0.05 - 1.40)	0.068
Fasting serum insulin	0.04 (-0.023 - 0.104)	0.212
Diabetes	1.42 (-1.10 - 3.94)	0.268
Probability of OSA	1.69 (-0.99 - 4.37)	0.216
	BT	
Serum BT	-0.238 (-0.497 - 0.02)	0.071
Diabetes	2.29 (-0.249 - 4.82)	0.077
Medication, urological	2.90 (-1.18 - 6.99)	0.163
	cBT	
cBT	-0.223 (-0.542 - 0.096)	0.17
Diabetes	2.52 (0.048 - 4.99)	0.046
	FT	
FT	-0.003 (-0.008 - 0.003)	0.339
Fasting serum triglycerides	0.642 (-0.078 - 1.36)	0.081
Fasting serum insulin	0.036 (-0.026 - 0.098)	0.257
Diabetes	1.81 (-0.708 - 4.32)	0.159
Probability of OSA	2.05 (-0.767 - 4.87)	0.153
	SHBG	
SHBG	0.035 (-0.013 - 0.083)	0.156

Fasting serum insulin	0.049 (-0.014 - 0.112)	0.124
Probability of OSA	2.00 (-0.738 - 4.73)	0.152
Medication; Met. Endo. Nut.	1.36 (-0.116 - 2.83)	0.071

Table 5.5.12 Predictive models of serum testosterone and SHBG with BDI score

in men aged 35 – 80, recruited from randomly selected households in North and West Adelaide. Data presented are stratified and probability weighted for age and geographical sampling region as described in Chapter 4.0. Total T model: F(6, 383) = 4.32, P = 0.0003, R2 = 0.10. BT model: F(3, 387) = 4.14, P = 0.007, R2 = 0.03. cBT model: F(2, 388) = 2.74, P = 0.066, R2 = 0.02. FT model: F(5, 384) = 3.71, P = 0.0031, R2 = 0.08. SHBG model: F(5, 384) = 4.32, P = 0.008, R2 = 0.09.

DISCUSSION

This chapter reports the cross-sectional associations of serum testosterone and SHBG levels with various clinical measures of neuropsychological function, including visuospatial function, memory and mood. Serum testosterone and SHBG levels were not associated with any of the measures of neuropsychological function performed in this study. However, there was a definite trend towards an association between lower serum levels of bioavailable testosterone and greater levels of depression, as measured by the Beck Depression Inventory, independent of potential confounders. An association between these two variables has previously been reported, cross-sectionally, in American men [50]. The major predictors of higher depression scores in the present study were having anxiety, asthma and insomnia. Cross-sectionally, salivary testosterone has also been shown to be associated, in a curvilinear manner, to spatial cognitive ability [86, 159].

Higher serum BT but not total T levels were associated with better cognitive test scores in older men [301]. Moreover, exogenous testosterone administration increased cognition in some, but not all, studies [3, 141, 302, 303]. Disagreement between studies is related, in part, to differences in the tools used to assess the various domains of cognitive function. Testosterone appears particularly to improve spatial memory [85]. These findings are in concert with bioavailable testosterone correlating with longitudinal memory decline in older males [72, 84]. Moreover, the neurological mechanisms responsible for learned (explicit) memory differ from those of implicit memory and studies of the effect of testosterone on memory must clearly identify the type of memory assessed. Testosterone improves memory in the SAMP8 mouse, an animal model of amyloid-beta protein overproduction [304-306]. In tissue culture testosterone reduces the production of

amyloid precursor protein [307]. Low testosterone, perhaps particularly free testosterone levels, are associated with the future development of Alzheimer's disease [308, 309].

Importantly, higher fasting serum triglycerides were associated with poorer TMT-B:TMT-A ratio's (indicating poorer executive function) and with higher depression scores. Hypertriglyceridemia is common in diabetics and is associated with cognitive dysfunction [310]. Lowering triglyceride levels with gemfibrozil enhances cognition [311]. Moreover, having diabetes and/or higher HbA1c levels was associated with slower finger tapping and higher depression scores. People with diabetes show accelerated cognitive decline. Hyperglycemia produces decreases in learning ability and memory in both rodents and humans [312-314]. Normalisation of glucose levels results in a reversal of these problems [315]. Diabetics have an increase in vascular lesions in the central nervous system which leads to cognitive decline [316]. Peripheral administration of DHEAS improves learning and memory retention in the SAMP8 mouse but not in streptozotocin induced diabetic CD-1 mice [317], suggesting that androgen permeability of the blood-brain-barrier is altered in diabetes, providing a mechanistic link between lower androgen levels and cognitive decline in diabetes. Moreover, hypertriglyceridemia produces leptin resistance at the level of the blood brain barrier [318]. Leptin enhances long term potentiation in the hippocampus, suggesting that it plays a role in memory functioning [319]. Total testosterone is inversely associated with leptin in humans [34, 225] and testosterone deficiency may lead to leptin and insulin resistance through increased abdominal adiposity[320], supporting another mechanism by which testosterone may influence central nervous system processes. Recently, it has been suggested that hyperinsulinemia may accelerate the development of Alzheimer's disease [321-324] because insulin degrading enzyme also degrades amyloid beta protein. The major associations with indicators of poorer memory in the present study were lower physical activity levels, insomnia and depression, whilst osteoarthritis, neurological health conditions and taking urological

medications were associated with better memory performance. The present study did not measure serum leptin levels.

Slower finger tapping speed, a general measure of brain injury was associated with being older and having a lower income and level of education. Surprisingly, poorer performance on the memory test and depressed mood were not associated with older age.

Taken together, these data indicate that diabetes and hypertriglyceridemia are independently associated with poorer cognitive outcomes. In addition, androgens may impact on cognitive function through improved glycaemic control or effects on serum triglycerides and leptin at the blood-brain-barrier. Mood may be associated independently with bioavailable testosterone levels and the present study shows a positive trend towards this association. The presence of anxiety, asthma and insomnia as well as diabetes and hypertriglyceridemia were also major factors in higher depression scores. Demographic factors such as age, income, education and pension status variably modified associations with some neuropsychological functions.