

Marginal selenium status in northern Tasmania

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Abstract

Se plays many important roles in humans. Marginal Se status has been associated with adverse health effects including an increased risk of chronic disease such as cancer. There are few Australian data, but the population of Tasmania, Australia, is potentially at risk of marginal Se status. A cross-sectional study of 498 men and women aged 25–84 years was undertaken to assess the Se status of the northern Tasmanian population. Se status was assessed using dietary estimates and measures of serum Se and glutathione peroxidase (GPx). Mean Se intakes were 77·4 (sd 31·3) and 65·1 (sd 23·7) µg/d for men and women, respectively; 27% of the subjects consumed less than the Australian/New Zealand estimated average requirement. Mean serum Se concentration was 89·1 (sd 15·1) µg/l; 83% of the study subjects had serum Se concentrations below 100 µg/l and 60% had serum Se concentration below 90 µg/l, suggesting that Se status in many subjects was inadequate for maximal GPx activity. This was supported by the positive association between serum Se and serum GPx ($P<0·001$), indicating that enzyme activity was limited by Se concentrations. The lowest mean serum Se concentrations were observed in the oldest age ranges; however, the prevalence of marginal Se status was similar across age ranges and did not appear to be influenced by sex or socio-economic status. The prevalence of marginal Se status was high in all sex and age subgroups, suggesting that the northern Tasmanian population could benefit from increasing Se intakes.

Key words: Selenium; Australia; Population studies; Dietary intake

Se is an essential component of at least twenty-five selenoproteins in humans. These proteins include the glutathione peroxidase (GPx), iodothyronine deiodinase and thioredoxin reductase enzyme families, which play important roles including antioxidant protection and thyroid metabolism^(1,2). Se also appears to be important for immune function⁽³⁾ and inflammatory response⁽⁴⁾.

Populations in most regions of the world consume sufficient Se to avoid diseases associated with overt deficiency such as Keshan disease and Kashin–Beck disease^(5,6). However, it has been suggested that in many countries, based on estimated frequencies of low plasma or serum Se concentrations, 50% or more of the population could have nutritional Se deficiency⁽⁵⁾, which may have adverse effects on health.

There have been a number of studies on the effect of marginal Se status on health and the potential benefits of increasing Se status⁽⁶⁾, and attention has centred on associations with cancer. Associations between lower Se status and increased cancer incidence were first observed in geographical studies in the USA and China^(7,8). Results from a number of case–control and intervention studies^(9–16) have supported these findings, but not all have done so^(17–19), and the only large randomised

controlled trial, to date, has failed to detect a protective effect⁽²⁰⁾.

Se status of the population is primarily influenced by the Se content of food supply, which is directly related to the Se levels in soils on which crops and livestock are raised. Low Se status of the population has been reported in areas with low soil Se in New Zealand, Europe and certain provinces of China⁽⁵⁾. In Tasmania, the southernmost state of Australia, most farming districts have experienced Se deficiency in livestock⁽²¹⁾, and, as a result, the human population is considered to be at risk of suboptimal Se status.

Studies of Se status in human populations in Tasmania have so far been very limited and have provided conflicting results^(22–24). The objective of the present study was to assess the Se status of a sample of the northern Tasmanian population.

Subjects and methods

The present study was cross-sectional in design. Recruitment was via mail, from an extract of the Australian electoral roll provided by the Australian Electoral Commission. The sample consisted of 192 men and 306 women residing in

Abbreviations: GPx, glutathione peroxidase; SEIFA, socio-economic indexes for areas; TAS, total antioxidant status.

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north, northwest and northeastern Tasmania. Subjects were 25–84 years old, free from significant illness and selected from the Australian Bureau of Statistics, Statistical Local Areas that were close to phlebotomy centres. The region in northern Tasmania from which the sample was drawn has a population of 126 958 residents >25 years of age, 52% of whom are female and 40% aged 55–84 years.

Subjects completed questionnaires to collect demographic, anthropometric and lifestyle information. A semi-quantitative FFQ was used to collect dietary data. Se intakes were calculated from responses using Nutrient Data Table (NUTTAB) 2006 food content values⁽²⁵⁾. Subjects attended phlebotomy centres in their local area to provide a venous blood sample, which was collected into trace element-free serum and serum separation vacutainer tubes (SST; Becton Dickinson, Rutherford, NJ, USA). Socio-economic status of subjects was estimated using the socio-economic indexes for areas (SEIFA) index for the area (Australian Bureau of Statistics Collector District) where each subject resided. The SEIFA index was derived from Australian Census variables related to both advantage and disadvantage, including households with low or high income, unemployment rates and proportions of people with limited or higher education⁽²⁶⁾. A lower SEIFA score in a given census district indicates that the district is relatively disadvantaged compared with the one with a higher score.

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Human Research Ethics Committee (Tasmania). Written informed consent was obtained from all subjects.

Procedures

Following venepuncture, blood samples were separated within 24 h by refrigerated centrifugation for 15 min at 1335 g. Aliquots of serum were stored at –80°C until analysis. All laboratory glassware, consumables and storage vessels used for trace element analysis were washed with 1% HNO₃ before use.

Serum Se concentration was determined by Zeeman-corrected graphite furnace atomic absorption spectrometry using a Spectra 640Z spectrophotometer (Varian, Inc., Palo Alto, CA, USA), and by the method of Saeed *et al.*⁽²⁷⁾. Analysis of Seronorm Trace Elements control serum (Sero, Billingstad, Norway) with a certified Se concentration of 72.6 µg/l gave a mean of 69.5 µg/l (CV 7.0%; *n* 19). Intra-assay precision was 3.7% (*n* 15).

Serum GPx was analysed on the DataPro clinical analyser (Thermo Electron Corporation, Melbourne, VIC, Australia) using a commercial reagent (Ransel; Randox Laboratories Limited, Crumlin, County Antrim, UK) based on the coupled enzyme assay by Paglia & Valentine⁽²⁸⁾. Inter- and intra-assay precision was 4.3% (*n* 21) and 3.0% (*n* 14), respectively.

Analysis for total antioxidant status (TAS) was performed on the DataPro clinical analyser (Thermo Electron Corporation) using the TAS reagent kit (NX2332; Randox Laboratories Limited). This method measured inhibition of the

formation of the 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical ABTS⁺, the level of which was proportional to the concentration of antioxidants in the sample. Randox TAS control serum was used for quality control; inter- and intra-assay precision was 2.8% (*n* 17) and 2.8% (*n* 20), respectively.

Serum total cholesterol, HDL-cholesterol, LDL-cholesterol and TAG were measured on the DataPro clinical analyser using standard enzymatic kits (Thermo Electron Corporation). Inter (*n* 17)- and intra (*n* 11)-assay precision for all serum lipid analyses was <4%.

Statistical analysis

Differences in Se status within groups as defined by age, sex or smoking habit were estimated using general linear modelling (STATA version 9.2; StataCorp LP, College Station, TX, USA). Post-estimation Holm's test analysis was then used to adjust *P* values for multiple comparisons⁽²⁹⁾. The relationship between serum Se with dietary and other biochemical factors was adjusted for smoking, age and sex, and examined using general linear modelling. The validity of regression assumptions was tested by *post hoc* analysis to exclude significant heteroskedasticity and missing variable effects.

A serum Se concentration of about 100 µg/l has often been suggested to meet the physiological requirement for GPx^(5,30,31); however, this threshold level may be as low as 80–90 µg/l^(32,33). In the present study, we used both concentrations as cut-off points to assess the Se status of the population sample.

Due to the variation in response from different age and sex subgroups in the study sample, a population estimate was made that was weighted for age, sex and socio-economic status, using data from the 2006 Australian Census for this region.

Results

Subject characteristics

A total of 2545 people were contacted by letter, resulting in 520 positive responses (20%); twenty-two subjects subsequently withdrew from the study. Response rates from the different age, sex and socio-economic status groups varied significantly (*P*<0.001), resulting in a greater than expected proportion of women, older subjects and those with higher than average socio-economic status. The mean age of subjects was 57.4 (sd 12.3) years; 65% of subjects were >55 years of age (Table 1). Mean BMI was 26.9 kg/m²; 62% of subjects had a BMI >25 kg/m² and 25% had a BMI >30 kg/m². A total of thirty-nine subjects were current smokers (male *n* 9 and female *n* 30).

Regular consumption of multivitamin and mineral supplements was reported by 23 and 19% of subjects, respectively. Only 8% of subjects consumed supplements which contained Se.

Table 1. Anthropometric, dietary and biochemical indices of the study subjects
(Mean values and standard deviations)

	Men (n 192)		Women (n 306)		<i>P</i> *
	Mean	SD	Mean	SD	
Age (years)	58.9	12.2	56.5	12.2	
Weight (kg)	86.2	15.1	70.6	14.8	
Height (cm)	176.6	7.9	163.3	7.3	
BMI (kg/m^2)	27.7	4.6	26.5	5.2	
Dietary intakes					
Energy (MJ)	9.11	2.72	6.81	2.29	<0.001
Se ($\mu\text{g}/\text{d}$)	77.4	31.3	65.1	23.7	<0.001
Body weight adjusted ($\mu\text{g}/\text{kg}$)	0.92	0.37	0.95	0.39	0.392
Energy adjusted ($\mu\text{g}/\text{MJ}$)	8.7	2.6	9.9	2.9	<0.001
Biochemical analysis					
Serum Se ($\mu\text{g}/\text{l}$)	88.9	16.0	88.3	14.6	0.776
Serum GPx (U/l)†	901.3	132.7	893.2	139.8	0.515
TAS (mmol/l)	1.45	0.20	1.36	0.17	<0.001
Total cholesterol (mmol/l)	5.51	1.16	5.83	1.14	0.002
HDL-cholesterol (mmol/l)	1.22	0.31	1.52	0.35	<0.001
LDL-cholesterol (mmol/l)	2.94	0.86	2.96	0.87	0.800
TAG (mmol/l)	2.32	1.73	1.79	1.10	<0.001

GPx, glutathione peroxidase; TAS, total antioxidant status.

* Variables were compared using general linear modelling.

† 1 U/l = 0.0167 $\mu\text{Kat}/\text{l}$.

Selenium intakes

Mean Se intake in men was 19% higher than in women ($P<0.001$); the difference was not statistically significant when expressed as intake per kg of body weight; however, women consumed significantly more Se per MJ of energy than men ($P<0.001$; Table 1).

Se intakes did not vary significantly among the different age ranges in either sex (Table 2). The lowest Se intakes were observed in men aged 75–84 years and women aged 45–54 years. The highest Se intakes for both sexes were in younger age ranges: 35–44 years in men and 25–34 years in women.

Significant differences in absolute intakes were observed between men and women aged 35–74 years (Table 2).

Mean Se intakes in current smokers were lower, but not significantly, than in non-smoking subjects (63.8 v. 70.4 $\mu\text{g}/\text{d}$; 95% CI of difference –5.1, 14.3; $P=0.352$).

Similar proportions of men (28%) and women (26%) consumed less than the Australian estimated average requirement (60 and 50 $\mu\text{g}/\text{d}$, respectively)^(3,4). The age range of 25–34 years had the lowest proportion of subjects consuming less than the estimated average requirement (18%), while the three oldest age ranges (55–64, 65–74 and 75–84 years) had the highest proportions of subjects consuming below the estimated average requirement (29, 28 and 29%, respectively).

Serum selenium

Mean serum Se concentration was 89.1 (SD 15.1) $\mu\text{g}/\text{l}$ (range 45–178 $\mu\text{g}/\text{l}$); overall, there was no significant difference between men and women (Table 1). The lowest serum Se in both sexes was observed in subjects aged 75–84 years. The highest mean serum Se was observed in younger men aged 25–34 years, while women aged 55–64 and 65–74 years had the highest concentrations (Table 2). Comparisons between the age ranges were significant in women but not in men. Between-sex differences for each age range were only significant in the age range of 25–34 years ($P=0.024$; Table 2).

Serum Se was lower in smokers compared with non-smokers (84.5 v. 89.3 $\mu\text{g}/\text{l}$; 95% CI of difference 1.2, 8.4; $P=0.013$), a difference that was reflected in serum GPx (847.3 v. 901.7 U/l; 95% CI of difference 22.3, 110.6; $P=0.003$).

Subjects who reported regular use of supplements containing Se had a mean serum Se nearly 10% higher than non-users (97.0 v. 88.3 $\mu\text{g}/\text{l}$; 95% CI of difference 3.1, 14.2; $P=0.002$). Regular consumers of Brazil nuts (unspecified amount) also had a 15% higher mean serum Se concentration compared with other subjects (103.0 v. 88.5 $\mu\text{g}/\text{l}$; 95% CI of difference 5.3, 23.6; $P=0.002$).

Table 2. Selenium intakes and serum selenium concentrations in age subgroups†
(Mean values, standard deviations, medians, number of subjects and 95% confidence intervals)

Age (years)	Men				Women				Difference	95% CI	<i>P</i>
	n	Mean	SD	Median	n	Mean	SD	Median			
Se intake ($\mu\text{g}/\text{d}$)											
25–34	9	69.0	12.4	68.7	19	70.3	31.8	64.8	1.3	–14.8, 17.5	0.872
35–44	18	87.3	40.0	73.6	37	65.3	20.7	59.0	22.0	–41.3, –2.7	0.025
45–54	29	84.2	32.3	75.4	58	61.9	21.1	58.7	22.2	–35.2, –9.2	0.001
55–64	60	76.4	34.1	71.3	100	65.5	26.6	61.5	10.9	–20.9, –0.9	0.033
65–74	64	75.4	28.4	69.4	80	65.2	21.0	64.9	10.2	–18.5, –18.6	0.017
75–84	11	68.7	21.1	67.6	10	68.4	23.8	67.1	0.3	–19.1, 18.6	0.976
Serum Se ($\mu\text{g}/\text{l}$)											
25–34	9	97.9	13.4	97.9	19	85.3	15.0	81.3	12.6	–22.9, –1.6	0.024
35–44	18	89.2	13.4	91.6	37	88.4	22.1	84.5	0.8	–10.3, 7.9	0.807
45–54	29	94.8	22.1	93.2	58	88.4	10.3	86.1	7.1	–15.0, 1.6	0.103
55–64	60	87.6	15.8	85.3	100	90.9*	13.4	87.6	3.2	–1.6, 7.1	0.192
65–74	64	86.9	13.4	87.6	80	91.0**	14.2	89.2	3.9	–0.8, 8.7	0.068
75–84	11	83.7	17.4	79.7	10	79.7	11.1	84.5	3.2	–15.0, 8.7	0.577

Mean values were significantly different from women in the age range of 75–84 years: * $P=0.017$, ** $P=0.021$.

† Comparisons were made between the age ranges in each sex and between the sexes in each age range using general linear modelling.

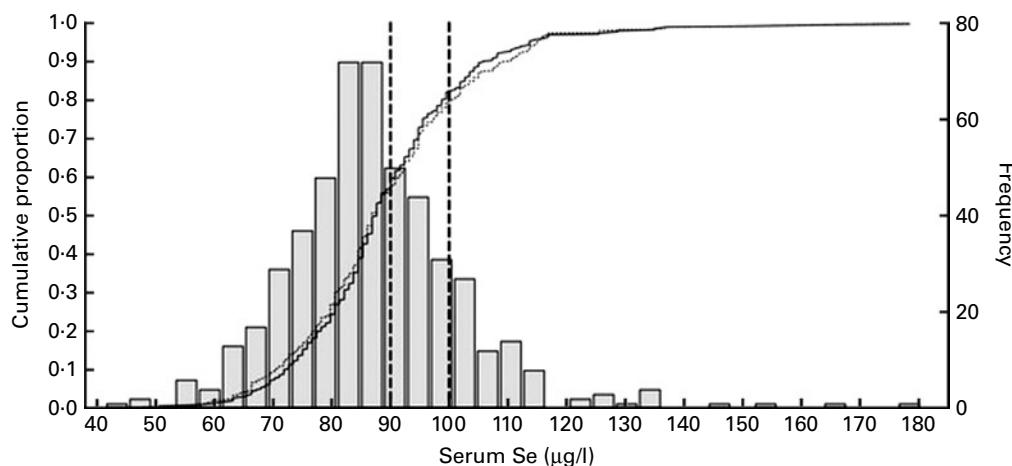


Fig. 1. Frequency distribution (histogram), and cumulative proportion (lines) of sample (—) and adjusted population (.....) estimates of serum Se in northern Tasmania. Dashed vertical lines indicate potential target concentrations (90 and 100 µg/l) for maximal glutathione peroxidase activity.

The distribution of serum Se concentrations is shown in Fig. 1; 83% of subjects had serum Se concentrations below 100 µg/l, while 60% of subjects had serum Se concentrations below 90 µg/l. Accordingly, serum Se concentration was observed to have a significant positive association with serum GPx activity ($\beta = 1.5$; $P < 0.001$), indicating that in many subjects, enzyme activity was dependent on serum Se concentrations.

In the adjusted population estimates (Table 3), the prevalence of low Se intakes and serum Se levels below the threshold values was not significantly different compared with the study sample.

Other associations

Serum Se had positive associations with serum HDL-cholesterol ($\beta = 7.5$; $P < 0.001$) and serum total cholesterol ($\beta = 1.5$; $P = 0.014$). Serum GPx activity was positively associated with serum HDL-cholesterol ($\beta = 75.3$; $P < 0.001$) and negatively associated with serum TAG ($\beta = -11.45$; $P = 0.038$). Other factors associated with serum Se were body weight ($\beta = -0.1$; $P = 0.012$), BMI ($\beta = -0.3$; $P = 0.008$) and serum TAS ($\beta = 8.5$; $P = 0.015$).

Adjusted dietary intakes of Se (µg/kg per d) were positively associated with serum HDL-cholesterol ($\beta = 0.16$; $P = 0.008$)

and negatively associated with serum TAG ($\beta = -0.33$; $P = 0.042$).

Socio-economic status was not significantly associated with dietary intake estimates or biochemical markers of Se status.

Discussion

Selenium intakes

A quarter of all subjects reported intakes less than the estimated average requirement for Se. A much greater proportion had marginal serum Se concentrations, the proportion varying between 83 and 60%, depending on the cut-off value that was used.

The discrepancy between the proportion of low Se intakes and low serum Se concentrations in the present study was potentially due to an overestimation of Se intakes arising from the use of Australian food content data⁽²⁵⁾, in the absence of Tasmanian data. As this database contains food content data from various sources, it cannot be truly representative of Tasmanian food content, leading to possible inaccuracies in intake estimations. In addition, even if validated for Se, the data collection method used, FFQ, has potential shortcomings, reviewed previously^(35,36), that may affect the accuracy of intake estimates.

Table 3. Estimates of population proportions with intakes below the Australian/New Zealand estimated average requirement (EAR) and with serum selenium below potential thresholds associated with maximal glutathione peroxidase activity (Mean values, standard deviations, proportions, 95% confidence intervals and risk ratios)

	Sample estimate	95 % CI	Population estimate	95 % CI	Risk ratio*	95 % CI	P
Se intake (%)							
<EAR	27	0.23, 0.32	24	0.23, 0.24	0.88	0.71, 1.09	0.24
Serum Se concentration (µg/l)							
Mean	89.1		89.2				
SD	15.1		15.8				
< 100 µg/l (%)	83	0.79, 0.86	80	0.76, 0.83	0.96	0.91, 1.02	0.26
< 90 µg/l (%)	60	0.53, 0.67	58	0.57, 0.58	0.96	0.87, 1.07	0.56

* Risk ratio was estimated by the Poisson regression adjusted for age, sex and socio-economic status.

Despite this, the estimates from the present study are the first reported for the Tasmanian population, and for men, these were considerably lower than the previously reported Australian intakes of 96⁽³⁷⁾ and 89 µg/d⁽³⁸⁾. In contrast, the estimates of 63⁽³⁷⁾ and 59 µg/d⁽³⁸⁾ for women from these two studies were similar to those for women in the present study. However, comparisons with these previous studies are problematic, as neither is recent and both have utilised direct food analysis of a representative diet rather than an FFQ used in the present study.

A significant influence on some subjects' Se intakes was Brazil nut consumption. The Se value of 920 µg/100 g in the food composition tables⁽²⁵⁾ shows the potential, as suggested previously⁽³⁹⁾, to significantly increase Se intakes if consumed regularly. In the present study, the 3% of subjects reporting regular intake of Brazil nuts had significantly higher serum Se than other subjects, with a mean above 100 µg/l.

Serum selenium

Given the strong positive association between serum Se and serum GPx activity, serum Se appears to be a more reliable indicator of Se status than dietary intakes in the present study.

The mean serum Se concentration was similar to the earlier published Tasmanian data of McGlashan *et al.*⁽²²⁾ of 80·5 µg/l from 171 female blood donors, while a much smaller sample of blood donors in the study of Daniels⁽²⁴⁾ had a mean serum Se concentration of 77·4 µg/l (*n* 25). Conversely, the most recent southern Tasmanian study of Jacobson *et al.*⁽²³⁾ has reported a considerably higher mean plasma Se concentration of 109·8 µg/l. Although different sample types (plasma *v.* serum) and analytical methods (inductively coupled plasma MS *v.* graphite furnace atomic absorption spectroscopy) were utilised in these two studies, they are unlikely to result in such a large difference. However, significant differences in Se status have been observed between close geographical regions in the same country in other studies^(40–42). Further research is required to determine whether this is also the case in Tasmania.

In comparison with the other Australian states, Se concentrations were similar between cohorts from South Australia⁽²⁴⁾ and New South Wales⁽⁴³⁾ (87·6 and 91·6 µg/l, respectively) but lower in more recent Queensland⁽⁴⁴⁾ and South Australian⁽⁴⁵⁾ studies (100 and 102·6 µg/l, respectively).

The mean Se concentration observed in the present study was higher than that reported from the South Island of New Zealand (66·3–77·4 µg/l)⁽⁴¹⁾, a close geographical neighbour with well-described low Se status. It was, however, similar to many European countries, where Se intakes are marginal⁽⁶⁾, and much lower than countries such as the USA, Canada and Venezuela⁽⁶⁾ with high Se intakes.

In the present study, there were varying response rates in different population subgroups; however, our adjusted population estimates (Table 3) suggested that the results from this sample are reasonably representative of the population of northern Tasmania, and therefore marginal Se status could be prevalent in this population.

Effect of age, smoking and socio-economic status

The lowest mean serum Se concentrations were observed in the oldest age ranges. Declining Se status with age has previously been observed^(13,46) and could be particularly important in populations with already marginal Se status, where it may contribute to a decline in health in older people, particularly considering its role in immune⁽³⁾ and antioxidant defence systems⁽¹⁾.

Smoking has also been associated with lower Se status in previous studies^(47–49); this may be because of decreased Se intake or an increased demand for Se due to increased oxidative stress from exposure to cigarette smoke. The cause of lower Se status in smokers in the present study seems at least partly related to a decreased Se intake, even though the relatively large intake differences between smokers and non-smokers were not statistically significant.

Observations of associations between higher socio-economic status and healthier diets have been made in Australia and elsewhere^(50,51); however, in the present study, socio-economic status (as measured by the SEIFA index) did not appear to be a significant factor influencing Se status. This lack of association with Se status is consistent with the observations in recent Tasmanian⁽²³⁾ and French studies⁽⁴⁰⁾ but is in contrast to some findings in Britain^(46,52).

Other associations with selenium

To date, findings regarding the relationship between the various indices of Se status and cardiovascular risk factors have been inconsistent. Several studies have reported positive associations between Se and serum lipids^(53–57), including each of serum total cholesterol, HDL-cholesterol, LDL-cholesterol and TAG⁽⁵⁶⁾, while others have found no association⁽⁵⁸⁾. In the present study, serum Se and serum GPx had modest associations with several lipid measures, as well as with body weight and BMI. The mechanisms for such associations with serum lipids are unknown; these may be due to the effects of selenoproteins such as GPx or iodothyronine deiodinase on lipid metabolism or simply the result of inter-related dietary exposures, as has been proposed previously⁽⁵⁶⁾; the latter could explain the significant associations found in the present study between intakes adjusted for energy and serum lipid components.

Serum TAS is a non-specific measure of antioxidant status. It was measured to determine whether any subgroups within the population sample had a different antioxidant status, and whether this was related to Se status. The sex differences observed in TAS have previously been reported⁽⁵⁹⁾, but TAS did not vary significantly in other groups, such as smokers. This could fit with the suggestion⁽⁵⁹⁾ that up to 50% of the variation in TAS results from additive genetic differences. Serum TAS in this sample was significantly associated with serum Se but not with GPx.

Chronic Se toxicity is thought to only occur at concentrations over 500 µg/l⁽⁶⁰⁾; the highest 5% of Se concentrations in northern Tasmania was 113–178 µg/l. Recent studies reporting associations between higher Se status and higher

lipid levels^(56,57) and also increased diabetes risk^(20,61,62) have prompted some concern over the potential adverse effects of increasing Se intakes, particularly in Se-replete populations, although the basis of such relationships remains unclear. Se concentrations in most of these studies are considerably higher than those observed in the present study, except the UK study of Stranges *et al.*⁽⁵⁷⁾.

Conclusion

The major finding from the present study was that a significant proportion of the northern Tasmanian population had Se concentrations below the physiological requirement for Se, regardless of which cut-off value was used. Furthermore, almost the entire sample (97%) had Se levels below 119 µg/l, which has been suggested as a target for maximising the chemopreventive effect of Se⁽⁵⁾.

With the importance of Se in many facets of health, including possible roles in the prevention of cancer and CVD, major burdens on health systems and particular concerns in the Tasmanian population⁽⁶³⁾, an increase in Se intakes could provide significant health benefits. However, due to the recent concern over the potential adverse effects of higher Se intakes, further large-scale studies in populations with marginal Se status, such as the long-proposed Prevention of Cancer by Intervention with Selenium (PRECISE) trial⁽³¹⁾, are required before current recommended intakes are increased.

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