Selenium & Preeclampsia: A Global Perspective

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Abstract

Preeclampsia is a complex multisystem disorder of pregnancy where oxidative stress plays an important aetiological role. The role of selenium in the synthesis of endogenous antioxidants is well documented, and a significant reduction in selenium has been reported in preeclamptic women. The objective of this study was to map global selenium status and preeclampsia incidence.

This study identified peer reviewed journal articles reporting national preeclampsia incidence (%) and matched these with reported values of selenium intake and plasma/serum selenium concentrations (μg/L). Matched data was obtained for 45 regions, reporting 6,456,570 births, spanning Europe, Asia, Australasia, Africa, North and South America. Increasing plasma selenium concentration was found to be correlated with a reduction in preeclampsia incidence (Pearson's r = -0.604, $P<0.0001$). Countries with a reported serum/plasma selenium level of ≥95 μg/L were considered selenium sufficient and a significant reduction in preeclampsia incidence for countries above this value (P=0.0007) was noted. Significant reductions in preeclampsia incidence were found to coincide with increases in plasma/serum selenium concentration in the New Zealand (P=0.0003) and Finland (0.0028) populations following Government intervention.

This study supports the hypothesis that selenium supplementation may be beneficial in reducing oxidative stress in women at risk of preeclampsia.

Introduction

Preeclampsia is a significant cause of maternal and perinatal mortality and morbidity, affecting an average of 3.45% of pregnancies globally [1]. Despite its prevalence, the exact causes of preeclampsia are still unclear; however, shallow trophoblast invasion and insufficient spiral artery remodelling are considered key early pre-clinical events that result in diminished placental perfusion and the generation of significantly increased levels of reactive oxygen species (ROS) within the preeclamptic placenta [2-4]. An imbalance between pro-oxidant ROS and endogenous antioxidant capacity is suggested as a possible factor in placental oxidative stress which results in increased trophoblast turnover and shedding of trophoblastic debris in to the maternal circulation [5-6]. There is an exacerbated maternal immune response leading to endothelial dysfunction and symptom manifestation in the preeclamptic patient [7-8].

Selenium is an essential trace element that is of significant importance to human health. A number of medical conditions have been associated with selenium deficiency [9] and there is increasing evidence to suggest that selenium deficiency may play a role in suboptimal cardiovascular [10], immune [11], and reproductive function [12-13]. The role of selenium is linked to its essentiality in the synthesis of numerous selenoproteins including the endogenous antioxidants Glutathione Peroxidase and Thioredoxin Reductase [9, 14], selenoproteins S, P and W and iodothyronine deiodinases [15]

Significant reductions in plasma [16-17] and toenail selenium [13] have been identified in preeclamptic patients, and coincide with observed reductions in endogenous antioxidant activity [8, 16] and increased levels of oxidative stress [2-3, 6, 8] in preeclampsia. The role of selenium and endogenous antioxidant proteins in the development and progression of preeclampsia is gaining favour in line with the oxidative stress hypothesis. Furthermore, other selenoproteins which may be depleted in preeclampsia could impact on the development and progression of the syndrome.

Selenium is generally obtained through the diet and regional variations in intake have been correlated geographically with soil selenium concentration, geochemistry, and rainfall [18]. A number of regions have been identified as selenium deficient with artificial increases in selenium intake instituted through soil and livestock selenium supplementation, agronomic biofortification [19-20] and the importation of high selenium wheat [21]. When considering the importance of selenium in reproductive health, combined with noted reductions in daily intake and selenium status in the UK [22] and other European populations [9] the benefit of selenium supplementation for pregnant women is increasingly being considered.

The current study aims to map the incidence of preeclampsia globally and match it to reported plasma and or serum selenium concentrations to further investigate the hypothesis that selenium supplementation during pregnancy may reduce the incidence of preeclampsia in populations with suboptimal dietary selenium intakes.

Experimental Methods

We searched PubMed, ScienceDirect and the Cochrane Library with the search terms "preeclampsia" and "hypertension and pregnancy", and cross-referenced them with the terms "epidemiology" and "incidence". A total of 2149 peer-reviewed articles were identified from which we restricted our search to studies reporting incidence data for individual countries. We also used Google searches to gain access to published perinatal statistics for Australia and New Zealand.

The Preeclampsia Community Guideline (PRECOG) [23] definition of preeclampsia as new onset hypertension diastolic ≥ 90 mmHg after 20 weeks gestation with new proteinuria determined as ≥1+ (0.3 g/L) on proteinuria dipstick testing, a protein/creatinine ratio of 30 mg/mmol or more on a random sample or a urine protein excretion of 300 mg or more per 24 hours was used as the standard diagnostic criteria for report inclusion in the current study.

Preeclampsia incidence data was then matched to peer-reviewed articles reporting daily selenium intakes and serum or plasma selenium concentration by country. We searched PubMed and Science Direct data bases using the search terms "selenium", "daily intake selenium", "serum selenium" and "plasma selenium concentration" and cross-referenced this to countries with reported preeclampsia incidence as identified in the previous search. We also searched the reference lists of articles identified by these search strategies and selected those that reported selenium concentration or intake. When multiple reports were found listing preeclampsia incidence or selenium data for a single country, results were combined to produce a weighted average value. If the study presented data for a particular region within a country we attempted to match this with reported selenium concentrations for the same region to exclude regional variations in selenium concentrations where possible. Reported values for daily selenium intakes were noted from papers that utilised both estimations from blood concentrations and dietary analyses and are presented together as estimated daily intakes.

Matched data was analysed using Predictive Analysis SoftWare (PASW) Statistics version 18.0.2 (SPSS Inc., an IBM Company, Chicago, USA). A two-sided Pearson analysis was used to determine any possible correlation between serum/plasma selenium concentration and reported incidence of preeclampsia in a global context. Further analysis of the data was performed using a two-tailed t-test after splitting the data set on the basis of a plasma selenium concentration of 95 µg/L that is considered indicative of maximal Glutathione Peroxidase activity [24]. Further analysis of the effect of increasing plasma selenium on the incidence of preeclampsia in the Finnish and New Zealand populations was also conducted using a two-tailed t-test. For all analyses a P value of

less than 0.05 was considered significant with figures reported as mean ± standard error of the mean (SEM).

Results

Matched preeclampsia and plasma selenium data was collected for 45 regions globally, spanning 35 countries from Asia, Europe, Africa, Australasia, North and South America. Data was ranked according to increasing serum/plasma selenium concentration and presented in Table 1. A total of 6,456,570 births were recorded in the preeclampsia studies reporting 222,812 preeclamptic births and a combined global preeclampsia incidence of 3.45% for the data set.

Country	Plasma Selenium (µg/L)	Estimated daily selenium intake (µg/day)	PET (%)	n	Reference
Egypt	46.9	49	9.2	3162	[25-27]
Nigeria	63.5	-	4.50	3926	[28-30]
New Zealand (Pre 1983)	53.9	27.4*	6.65*	10484	[31-41]
Greece	65.5	110-220	2.30	9915	[42-47]
Croatia	66.8	27.3	4.10	14003	[48-50]
Finland (pre 1985)	67.6	25-60	6.16*	1025339	[51-66]
Poland	68.3	30-40	4.40	4648	[43, 67-73]
Brazil	72	26.3	7.50	4892	[74-76]
Italy	72.8	43	3.75	8894	[44, 77-84]
India	73	28-105	4.18	29562	[85-90]
Denmark (1978-1983)	75.5	38-47	3.46	17457	[43, 91-95]
Ireland	77.2	44-51	2.20	1048	[96-100]
Hungary	77.4	41-90	3.05	36642	[101-105]
Iran - Tabriz	79	-	5.75	400	[106-108]
UK (1995-2005)	79.1	29-39	1.97	8366	[44, 109-112]
Spain	82.3	32	2.85	8295	[44, 113-114]

Sweden (1987-1993)	85	38	5.2*	10659	[43, 53, 115-120]
Germany	86	38-48	2.6	352698	[121-124]
Jamaica	86	-	4.60	6275	[125-126]
Belgium	90	28-61	5.80	274	[127-131]
Scotland	91	34.3	4.1	9057	[132-137]
Denmark (1996-2002)	94.2	68	2.22*	81708	[44, 138-145]
China- Shanghai	96.2	53-80	3.90	16936	[146-148]
Australia	96.7	55-87	3.2	208879	[20, 149-151]
Sweden (1992-2006)	97.6	38	2.9*	838528	[44, 152-156]
Mexico	100	61-73	5.50	41828	[157-159]
USA - NY	100.9	81	3.3*	703457	[160-169]
Netherlands	102	72	1.4	2413	[43-44, 53, 170-173]
Portugal	102	10-100	1.40	6276	[43, 174-175]
Saudi Arabia	103	75-122	2.80	705	[176-178]
Finland (post 1985)	106.6	67-110	1.96*	9216	[53, 58, 140, 179-188]
New Zealand (post 1983)	113	19-80	1.94*	330998	[21, 24, 189-202]
Norway	113.5	77	3.01*	1979859	[56, 203-214]
Canada - Ontario	115	98-224	3	386323	[215-220]
Israel	119	77.3	2.8	82436	[221-222]
Singapore	119	-	3.6	2213	[223-225]
Iran - Jahrom	119	-	3.3	2300	[108, 226]
UK (1970-1988)	120	60	3.1	15744	[43, 47, 227-234]

USA - MA	121	60-220	3.7	1096	[121, 235-238]
Japan	122	19-180	1.7	11311	[239-243]
Iran - Mashhad	122.7	-	3.6	83	[244-247]
Canada - Alberta	123.5	98-224	1.7	97270	[215-216, 248-249]
Canada - Montreal	146	98-224	2.2	5337	[215-216, 250-252]
Thailand	146	27-75	1.9	35923	[159, 253-254]
Taiwan	153.2	145.2	1.4	29735	[255-257]

Table 1. Global incidence of preeclampsia matched to reported plasma selenium concentration.

*Denote multiple reported values were utilised to calculate an average for the country.

n value represents patients in studies reporting incidence of preeclampsia.

PET % : Preeclampsia incidence represented as a percentage

Pearson correlation analysis demonstrated a significant correlation ($P<0.0001$) between increasing plasma selenium concentration and decreasing incidence of preeclampsia (Pearson r = -0.604, 95% CI = -0.377 to -0.462). This correlation is illustrated in Figure 1 with associated linear trend and 95% CI lines ($R^2 = 0.365$).

Activity of antioxidant seleno-enzymes is correlated to increasing selenium concentration both in cell culture and in animal [258-259] and human systems [35]. Plasma concentrations of approximately 95 (range 89-114) µg/L are considered adequate to maximise the activity of the endogenous antioxidant Glutathione Peroxidase [24, 260], however a plateau in Glutathione Peroxidase activity is not seen until plasma levels of 140 µg/L are reached [260]. In light of this information we split the data set into two groups using a plasma selenium concentration of >95 µg/L as indicative of seleno-sufficiency (Figure 2). By this criterion, 23 countries considered seleno-sufficient had a combined reported incidence of preeclampsia of 2.75% (SEM 0.210) that upon unpaired two sided t-test analysis was found to be significantly lower ($p<0.0007$) than the selenium deficient subset (n = 22) with a mean reported incidence of 4.39% (SEM 0.407).

A number of regions globally have been identified as having low soil selenium concentrations however it was not until the 1970s that health authorities around the world became concerned when

comparing daily intakes with those of the USA. In response to recognised deficiencies of selenium in the Finland population the Finnish government instituted compulsory soil selenium supplementation through fertilisation for cereal and grassland crops in 1985 and a significant increase in selenium status was achieved in the population [261-262]. New Zealand is also recognised as having low soil selenium and the population was recorded as having daily intakes similar to those in Finland [263]. In response, New Zealand took a more conservative approach and encouraged the supplementation of selenium in animal feeds in regions noted as deficient. Improvements in livestock selenium concentrations in combination with the deregulation of the importation of wheat from Australia and the USA and the increased availability of selenium-rich cereal products [21, 191] resulted in a significant increase in the selenium status of the New Zealand population [21].

To date the effect of increasing selenium supplementation on the incidence of preeclampsia in either population has not been reported. Reported statistics for each country were analysed pre and post selenium supplementation (Figure 3) and upon unpaired two-tailed t-test demonstrated significant reductions in the reported incidence of preeclampsia in both the New Zealand ($P=0.0003$) and Finland ($P=0.0028$) populations.

Finland was successful in reducing the incidence of preeclampsia by 61% from 5.24% prior to 1985 to 2.06% post selenium supplementation whereas a New Zealand noted a 71% reduction in the incidence of preeclampsia from 6.65% prior to supplementation in 1983 to 1.94% for the period 1985-2009. Interestingly the incidence of preeclampsia reduced to a similar level in both populations.

Discussion

Selenium is an essential micronutrient which has well documented benefits to both male and female reproductive health. For males, selenium is important for testosterone biosynthesis and the production and development of normal spermatozoa [264]. In females decreased concentrations of selenium have been linked to compromised fertility and early pregnancy loss in both animals [265] and humans [12]. There have been several reports of decreased selenium status in mothers presenting with preeclampsia including significant reductions in toenail [13] and plasma selenium concentrations [16-17]. There have also been reports of decreased selenoprotein production in preeclamptic pregnancy including important endogenous antioxidants, such as glutathione peroxidase and thioredoxin reductase [8, 16]. Given the importance of selenium in reproductive function this study investigated the nutritional selenium status of various populations and related that to the incidence of preeclampsia.

Geographical variations in soil selenium concentration are well documented and known to relate to plasma selenium concentrations regionally and within populations as demonstrated in the Iranian population where individuals in the North West of the country (Tabriz [106]) have lower selenium levels than those occupying the North Eastern (Mashhad [245-247]) and Southern (Jahrom [108]) regions of the country. Acknowledgement of the importance of selenium to human health, particularly cardiovascular disease and cancer prevention, sparked increased interest in population wide selenium status across the globe in the 1970s. Two key studies conducted in China [266] and New Zealand [267] provided the scientific basis for the establishment of recommended dietary allowances/intakes for females published in the United States (55 µg/day) [268], United Kingdom (60 µg/day) [269] and Australia (60 µg/day) [270]. There is a suggestion however that a conservative interpretation of the data was used [268] and that recalculation would suggest a much higher daily intake of 73 µg/day would be necessary to achieve a plateau in plasma Glutathione Peroxidase activity [9], a widely accepted biomarker of selenium status. A further increase to 80-100 µg/day would be needed if platelet saturation was considered as a measure of sufficiency [271]. The increased requirement of selenium during pregnancy and lactation is not under debate and all published RDI's recommend an increase in daily selenium intake by 10 µg/day during pregnancy and 15 µg/day during lactation to support the increased requirements of the fetus and newborn [122, 272-273]. The results of this study and those of others that have examined daily selenium intakes in various populations [9, 274] would suggest that a number of countries are consuming selenium at a suboptimal level and that during pregnancy, intakes are not high enough to maximise endogenous antioxidant activity.

Evidence relating to regional variations in preeclampsia incidence and underlying selenium status is sparse and in some respects not entirely validated. However, a 1990 study from China reported an increased incidence of pregnancy induced hypertension in a region of the country known to be selenium deficient [275]. The current analysis of 70 studies reporting preeclampsia incidence and of 166 studies reporting plasma and or serum selenium concentrations summarises the global incidence of preeclampsia as it relates to selenium status. A significant correlation ($P<0.0001$, Pearsons r = -0.604, 95% CI = -0.377, -0.762, R^2 = 0.365) was found suggesting increasing selenium status may be beneficial in reducing the incidence of preeclampsia particularly when plasma concentrations exceed the level considered necessary to achieve optimal Glutathione Peroxidase activity (95 µg/L).

The routine supplementation of selenium in New Zealand and Finland provides an important example of direct intervention in the food chain. Both these countries have been successful in increasing the selenium status of residents above the 95 µg/L level and the current analysis demonstrated an associated significant reduction in the reported incidence of preeclampsia (Figure 3). The scenario in neighbouring European countries differs in terms of preeclampsia incidence with an increasing incidence seen in Norway [58] (3.3% in 1970 to 4.5% in 2005) and the Netherlands (1.4% in 1992-1994 [171] to 3.5% in 2003-2004 [170]) and reductions in Denmark (3.5% in 1978-1983 [92] to 2.2% in 1996-2002 [138-139, 145]) and Sweden (5.2% in 1987-1992 [115] to 2.9% in 1992-1996 [152]). When changes in selenium for these countries over similar time period was recorded it was found that the daily intake or serum level of selenium was found to increase in those countries noting reductions in incidence of preeclampsia (Denmark; 78.5 µg/L [43, 93] to 94.2 µg/L [141-144] and Sweden; 85 µg/L [43, 116-119] to 97 µg/L [44, 155-156]) and decreased in those countries with increased incidence of preeclampsia (Netherlands; 72 µg/day [173] to 49 µg/day [140]). Although it may be interesting to speculate that the reduction in the incidence of preeclampsia noted in this study may be related to increasing selenium status, this result does not prove cause and effect as multiple factors are likely to play a role in the development and incidence of this complex disease on a population wide level. In addition, the incidence of other diseases such as cardiovascular disease [276] and some cancers [277] has similarly declined over the past 25 years with improvements in surveillance and provision of improved clinical care.

Routine utilisation of selenium-based fertilisers and food fortification has been demonstrated to increase population based selenium status; however dietary differences between individuals will result in variable intakes within a population. In addition concern surrounds mandatory supplementation due to the toxicity of selenium which may be reached in sensitive individuals at a level as low as 600 µg/day [278]. With this intake level in mind it is of interest that with the

exception of high selenosis areas, none of the regions reported previously [9, 263] or in the current analysis (Table 1) reach a level of selenium intake that borders on the even more conservative upper limit of selenium intake of 400-450 µg/day recommended by the World Health Organisation [279]. As such controlled selenium supplementation within a population, in this case to pregnant women could be suggested as a possible measure to improve seleno-sufficiency particularly in populations known to have low selenium status. This may be an important consideration in countries around the world such as Australia and the United Kingdom [9, 280] where reductions in soil and plasma selenium concentrations have been noted over an extended period [9, 20, 280].

There are limited studies available that report selenium supplementation during pregnancy. However, all published studies available to date have reported reductions in the incidence of hypertensive complications of pregnancy in those patients with increased selenium intake [246, 281-283]. The largest of these studies was an analysis of the effect of multivitamin use in the Danish National Birth Cohort (n=28,601) where a multivitamin supplement containing 50 µg selenium was most commonly taken [281]. Smaller studies that supplemented 100 µg Se/day as part of a single micronutrient [246] or a more comprehensive antioxidant supplement [282] also demonstrated benefit, with no reported adverse consequences related to supplementation at either of these doses. It is also interesting to consider that the reported reduction in preeclampsia risk observed in these studies through selenium supplementation has not consistently been reported for supplementation with other exogenous antioxidant molecules such as vitamins C and E [284-286].

Preeclampsia is a disease unique to the human species and higher order primates. Limited experimental models of the disease exist, however the removal of selenium from the diet of rats has been found to induce a hypertensive/proteinuric state during pregnancy similar to that of preeclampsia [258]. The placentae from these pregnancies also showed decreased expression of endogenous antioxidants such as GPx and Thioredoxin reductase and a concomitant rise in biomarkers of oxidative stress. Conversely, i*n vitro* and *in vivo* studies have demonstrated that selenium supplementation has a direct capacity to increase the activity of endogenous antioxidant enzymes [111] protecting placental tissue from oxidative damage. The importance of selenium to reproductive health may centre on the incorporation of selenium in the form of selenocysteine in the active site of endogenous antioxidant proteins such as Glutathione Peroxidase and Thioredoxin Reductase where it acts as a redox centre to combat oxidative damage from reactive oxygen species (ROS). However, other important selenoproteins may have a role to play in the etiology of preeclampsia including selenoproteins P, W and S. Interestingly, a recent publication has shown a genetic association between Selenoprotein S and the development of preeclampsia and has

postulated a role for this selenoprotein in the exacerbated inflammatory response associated development of the disease [287].

The current investigation has demonstrated globally, that a reduction in plasma selenium concentration is associated with an increased incidence of preeclampsia and that concentrations in excess of 95 µg/L may in fact be protective against the development of the disease. This study supports those previously reported that supplementing the diet of pregnant women with selenium [246, 281-283] may lower the incidence of preeclampsia and adds further weight to the current SPRINT (Selenium in Pregnancy Intervention) trial [288] running in the United Kingdom investigating the effect of 60 µg/day selenium on the risk of preeclampsia (principal investigator MP Rayman [13]). Selenium supplementation either alone or in combination with a general multi-nutrient supplement may have a significant effect on not only the incidence of preeclampsia, but may also delay the onset and severity of the disease, ameliorating placental oxidative stress and buying valuable time for fetal development prior to delivery. Selenium supplementation may provide a readily applicable method of lessening the impact of this disease, and this may have considerable benefits to populations, especially those in developing countries

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Figure 1. Effect of plasma selenium concentration on the incidence of preeclampsia. Plot includes linear regression line with associated 95%CI lines.

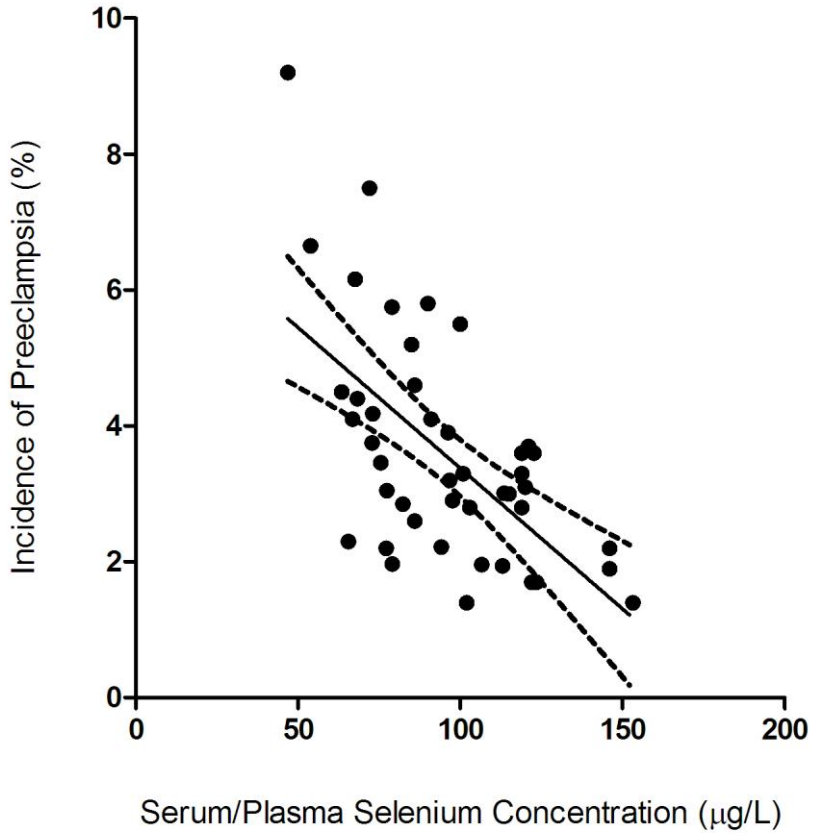

Figure 2. Comparison of the incidence of preeclampsia globally for countries split on the basis of selenium sufficiency. A selenium concentration of 95ug/L was used as the point at which populations were considered Seleno-Deficient (23 published studies) or Seleno-Sufficent (20 published studies).

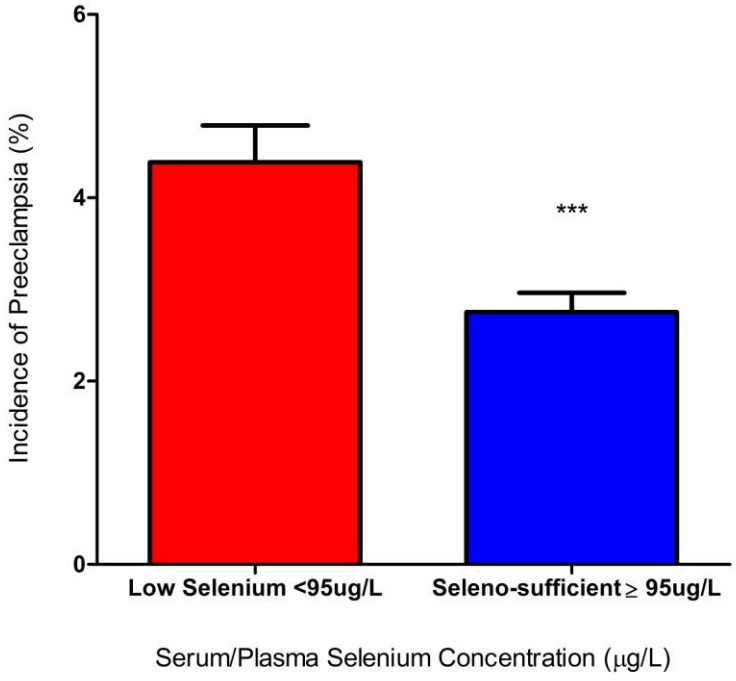
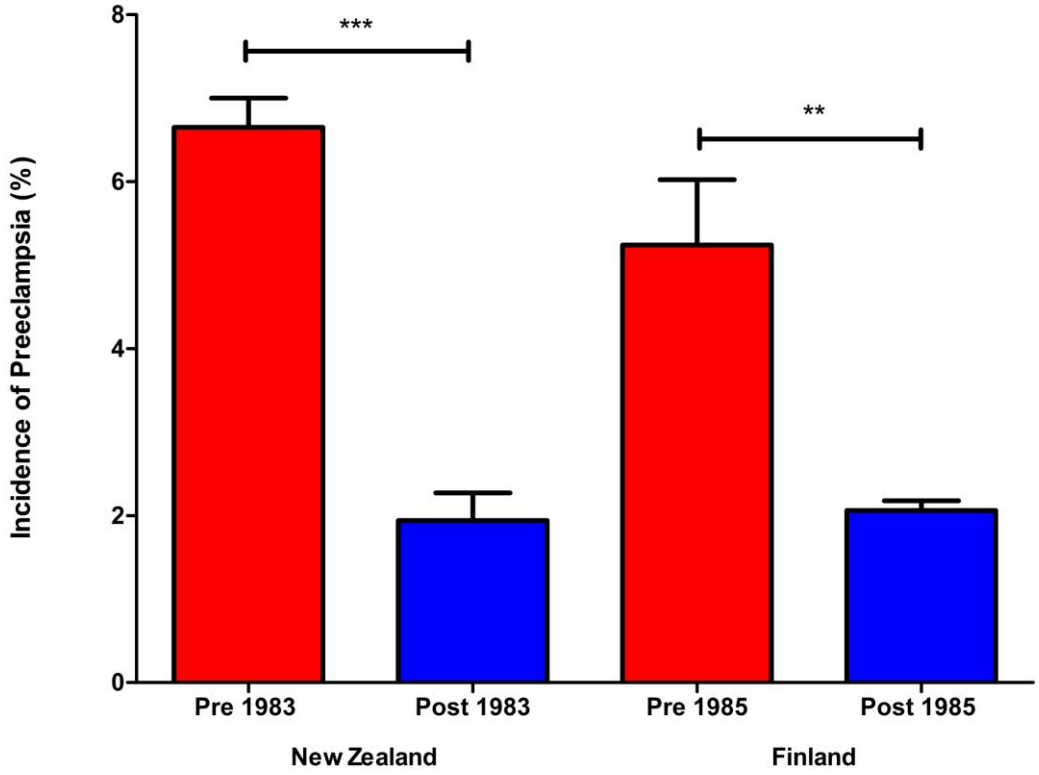
Figure 3. Comparison of the incidence of preeclampsia in the New Zealand and Finnish populations pre and post selenium supplementation.