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Dietary Iodine deficiency in the Gippsland region of Victoria, Australia

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Under Review

Rahman A, Chesters J, Gayle S, Deacon N (Under Review). Taking a history: The learnings that national health science forgot. The Australian Journal of Rural Health.

Rahman A, Deacon N, Panther B, Chesters J, Gayle S (Under Review). Is Gippsland environmentally iodine deficient? Water iodine concentrations in the Gippsland region of Victoria, Australia. The Australian Journal of Rural Health.

Rahman A, Gayle S, Deacon N, Chesters J, Panther B (Under Review). Urinary iodine deficiency in Gippsland pregnant women: The failure of bread fortification. Medical Journal of Australia.

TERMS USED IN THE STUDY

AMSIS	Australian Maritime Spatial Information System
ARROW	Australian Research Repositories online to the World
ATDS	Australian total Diet Study
CL	Confidence limit
CV	Coefficient of Variance
FSANZ	Food Standards Australia and New Zealand
Goitre	A thyroid gland that is enlarged
Hypothyroidism	Inadequate secretion of thyroid hormone
ICCIDD	International Centre for Control of Iodine Deficiency Disorders
IDD	Iodine Deficiency Disorders
IQR	Inter quartile range
MUIC	Median urinary iodine concentration
NINS	National Iodine Nutrition Study
SD	Standard deviation
Thyroid gland	Butterfly shaped endocrine gland in front of the neck
Thyroid hormones	Hormones secreted by thyroid gland (T3 and T4)
Thyroglobulin (Tg)	A precursor in the synthesis of thyroid hormone
Thyroxine supplements	Medications used for treatment of hypothyroidism as a replacement of thyroid hormone

TRH	Thyrotropin releasing hormone, secreted from hypothalamus
TSH	Thyroid stimulating hormone, secreted from anterior pituitary gland
T3	Triiodothyronine (thyroid hormone)
T4	Tetraiodothyronine/ Thyroxine (thyroid hormone)
UNICEF	United Nations Children's Fund
VCGS	Victorian Clinical Genetics Services
WHO	World Health Organization

ABSTRACT

Dietary Iodine deficiency in the Gippsland region of Victoria, Australia

Background

Iodine is an essential micronutrient for the production of thyroid hormones and normal neurodevelopment. A deficiency in iodine causes a number of defects collectively known as Iodine Deficiency Disorder (IDD). Even mild iodine deficiency in pregnancy is a risk factor for babies as it may result in impaired intellectual development; this is the most serious consequence of mild to moderate dietary iodine deficiency. Australia overall is iodine deficient. However, in the National Iodine Nutrition Study (NINS), Victoria had the worst status with regard to iodine deficiency in school children.

The Gippsland region of Victoria has a long history of iodine deficiency. In 1960, Gippsland was described in a WHO monograph series on endemic goitre as the 'home of goitre' in Victoria. Despite this history the Gippsland population has not been screened for iodine deficiency since 1948.

In response to this data we devised a four part study to provide details of the current regional and sub regional iodine status of Gippsland.

Hypothesis

There is a recurrence of dietary iodine deficiency in the Gippsland region.

Objective

The research plan initially included three objectives

- To examine the historical evidence of dietary Iodine deficiency.
- To research environmental iodine status.
- To estimate the population iodine status and factors affecting it.

Two further objectives were added during the project

- To develop an effective and easy method to regularly analyse and monitor the iodine status (deficiency) of pregnant women and their new born babies.
- To measure the effect on the iodine status of a cohort of Gippsland pregnant women of the recently commenced Food Standards of Australia and New Zealand (FSANZ) nationwide bread iodine fortification program.

Methods

This is a four part study using different methods to test our hypothesis:

- Part 1: Search for historical evidence of iodine deficiency using archival research, rare book and journal collection searches and asking for Gippsland people to recall previous iodine supplementation programs they may have participated in.

- Part 2: Research for environmental evidence of iodine deficiency by measuring the iodine concentration of drinking water from 18 water treatment plants and rain water tanks across central, west and south Gippsland.

- Part 3: Victorian (including Gippsland) Neonatal population iodine status estimation by retrospective neonatal Thyroid Stimulating Hormone (TSH) data analysis from 2001 to 2006.

- Part 4: Gippsland pregnant women iodine status estimation by urinary iodine concentration measurement and an exploration of factors influencing iodine status during pregnancy by application of a self-reported food questionnaire.

Results

There was an iodine tablet supplementation program in Gippsland schools from the late 1940s to late 1960s. Gippsland drinking water shows an iodine concentration indicative of environmental iodine deficiency. Analysis of the Victorian neonatal Thyroid Stimulating Hormone (TSH) database from 2001 to 2006 shows that the incidence of iodine deficiency is increasing in Gippsland and Victoria among newborns at the population level. The urinary iodine concentration in a cohort of Gippsland pregnant women indicates an inadequate intake of iodine during pregnancy and that the bread iodine fortification program appears to be ineffective in this cohort.

Conclusion

Results from this study indicate that dietary iodine deficiency is a reemerging problem in the Gippsland region. In Gippsland the assumption of the average Australian population daily intake of iodine through drinking water by FSANZ is misleading and FSANZ needs to take account of regional variation when calculating the influence of this critical dietary component. The current iodine fortification program needs to be extended to other foods and focus on the prevention of iodine deficiency during pregnancy. Neonatal TSH levels should be used to monitor the Australian population iodine (deficiency) status and the effectiveness of fortification, especially in the population groups most at risk of iodine deficiency.

PART A: GENERAL DECLARATION

Monash University
Monash Research Graduate School

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes one original paper accepted for publication in a peer reviewed journal and three papers submitted for publication. The core theme of the thesis is to research the historical and environmental evidence of iodine deficiency and population iodine status in the Gippsland region of Victoria, Australia. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Monash University Department of Rural and Indigenous Health under the supervision of Associate Professor Janice Chesters.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 3-6 my contribution to the work involved the following:

[If this is a laboratory-based discipline, a paragraph outlining the assistance given during the experiments, the nature of the experiments and an attribution to the contributors could follow.]

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
3	Taking a history: The learnings that national health science forgot	Under Review	80%: Study design, establishment of research database, writing and editing of the paper.
4	Is Gippsland environmentally iodine deficient? Water iodine concentrations in the Gippsland region of Victoria, Australia.	Under Review	80%: Study design, establishment of research database, performing the statistical analysis, writing and editing of the paper.
5	Increased iodine deficiency in Victoria, Australia: Analysis of neonatal TSH data 2001 to 2006.	In Press	80%: Study design, establishment of research database, performing the statistical analysis, writing and editing of the paper.
6	Urinary iodine deficiency in Gippsland pregnant women: The failure of bread fortification.	Under Review	80%: Study design, establishment of research database, performing the statistical analysis, writing and editing of the paper.

I have / have not (circle that which applies) renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed:
………………………………………………………………………

Date: ………………………………

ACKNOWLEDGEMENTS

Unlike many other students, my PhD started with me taking lessons from a driving instructor, (Sue Dietrich) so that I could obtain my driving licence. This was one of the major training needs I had in my PhD program. It helped me to drive thousands of kilometres across Gippsland to collect information and water and urine samples.

Like many other PhD projects, mine was not a smooth one. My supervisors, Associate Professor Janice Chesters, Dr. Nick Deacon and Dr. Gayle Savige were the people who constantly supported me in every possible way throughout the difficult 'journey' of my PhD. I gratefully acknowledge them for their kind consideration in choosing me as their student. I would also like to thank Dr Barbie Panther (School of Applied Science and Engineering, Monash Gippsland) for supervising me in the laboratory.

A PhD is usually regarded as an academic exercise to become an independent researcher. I have a feeling that my project at some point of time became a Gippsland 'people's project'. The support that I received from Gippslanders from all walks of life was invaluable. There was interest in this project from the common people. I remember a child (a regular co-passenger on local transport) who used to call me 'Doctor Boy' after watching me on the TV news, talking on iodine deficiency in Gippsland. Without active support from Gippsland residents, it would have been impossible to collect the information and data for this study.

Monash University Department of Rural and Indigenous Health (MUDRIH), Monash University Faculty of Medicine, Nursing and Health Sciences and School of Applied Science and Engineering, Monash University Gippsland have provided me with support for my study. Though we tried to keep the cost of running the sub studies at a minimum, it required a fairly good amount of financial and in kind assistance from Monash to undertake such a comprehensive iodine study. The SAS

Fellowship Award by SAS Inc. Australia, Travel awards from the Nutrition Society of Australia and from Monash all helped me to develop my PhD.

Dr. Simon Kitto and Dr. Sharafat Malek (MUDRIH) were my initial Monash contacts before I started my candidature. I gratefully acknowledge their contribution that led me to enrolling at Monash. Helen Chambers (MUDRIH) used her well practised expertise to speedily manage the formatting of the thesis. Julie Irvine (MUDRIH) was a regular supporter of this PhD project and she professionally managed all the important calls and messages coming in while I was out in the field collecting samples.

I also would like to thank all my family members, specially my parents and sisters for keeping their trust in me. The mental support they offered me was really very much needed.

Finally, my dear wife, Dr. Rumana Hafiz and my daughter and son, Nazifa and Ahnaf suffered most during the tenure of my candidature and have always been a source of inspiration to me to complete the PhD. I dedicate this thesis to my wife and children.

CHAPTER 1

General introduction

This thesis is a comprehensive study of dietary iodine deficiency in the Gippsland region of the State of Victoria. The data was all collected and analysed between 2007 and 2010. The research evolved into a four part study which looked at the historical evidence of iodine deficiency; environmental evidence of iodine deficiency; population iodine status and finally a study on the effectiveness of the national iodine fortification program to prevent iodine deficiency among pregnant women.

As this is a thesis by publication four of the chapters are papers which are either in press or submitted to quality Australian journals. The relevant Australian and international literature is discussed in each paper. The purpose of this introductory chapter is to outline the rationale, hypothesis and objectives of the thesis as a whole. This chapter reviews the importance of the focus on iodine deficiency and the rationale for studying the Gippsland region. Finally a chapter outline for the entire thesis is provided.

Why research iodine deficiency

Iodine (atomic weight 126.9 g/atom) is an essential micronutrient for the production of thyroid hormones. Thyroid hormones, secreted from thyroid glands, regulate the metabolic pattern of cells in the body and play a crucial role in the process of early growth and development of most organs, especially the brain[1-3]. A lack of iodine in the diet leads to an inadequate secretion of thyroid hormone (known as hypothyroidism), which in turn causes a number of symptoms collectively known as Iodine Deficiency Disorder (IDD). IDD can affect people of any age. The adverse effect of IDD can start as early as the foetal stage, as the foetal iodine status depends on the presence of an adequate amount of iodine in the mother's diet[4]. If iodine deficiency occurs during the most critical period of brain development (from the foetal stage up to the third month after birth), the resulting thyroid failure will lead to irreversible alterations in brain function[5,6]. Therefore studying iodine deficiency is an important public health research topic. Figure 1 provides a summary of thyroid hormone production and regulation.

Figure 1: Thyroid hormone production and regulation (adopted from Stanbury JB, 1960[7])

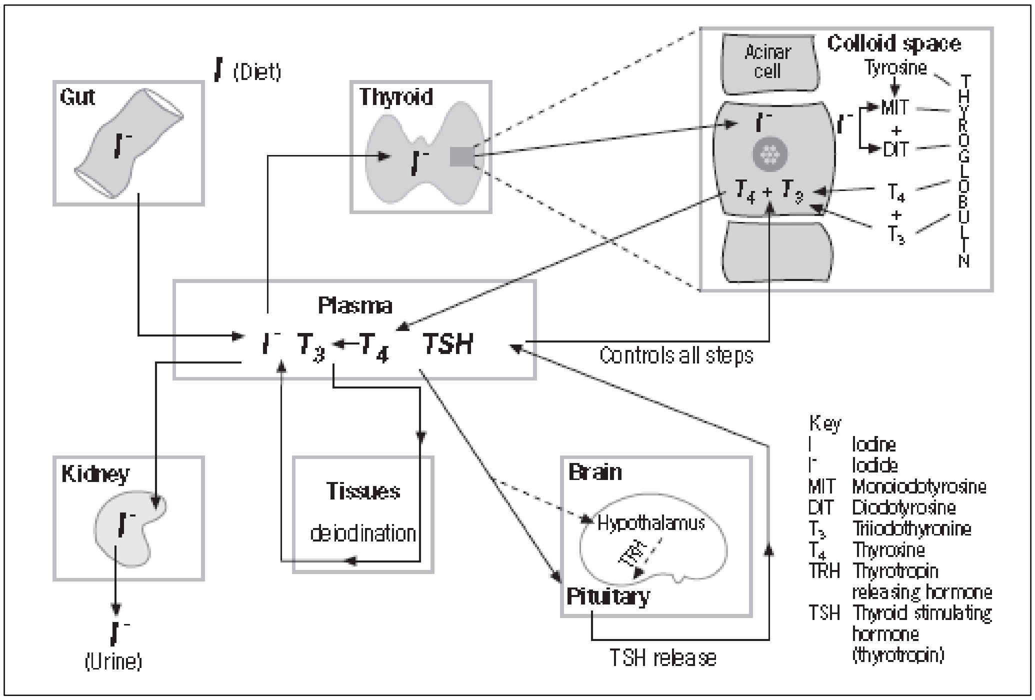
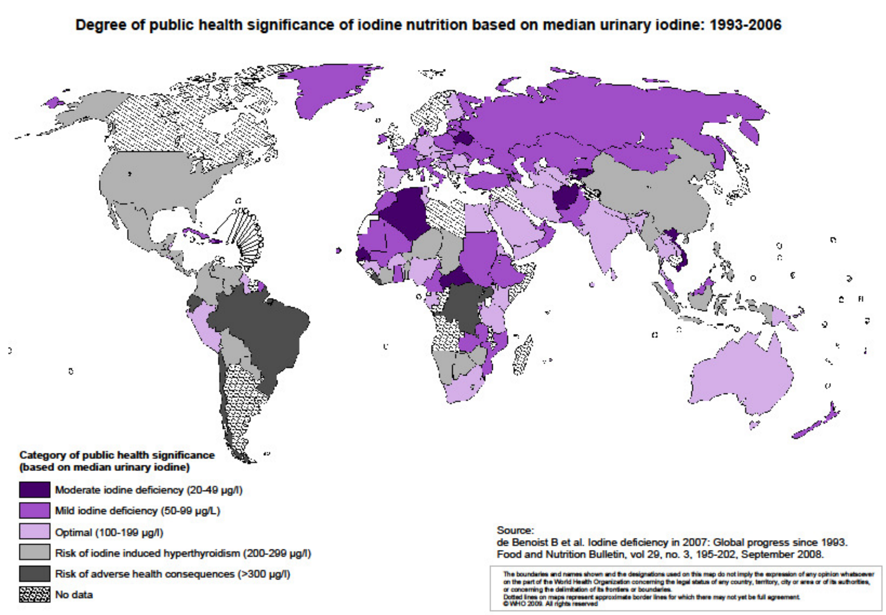


Figure 2: Iodine status worldwide based on median urinary iodine concentration (adopted from Beonist B et al, 2008 [9])



The World Health Organization (WHO) have published credible research that demonstrates iodine deficiency can cause a loss of 10-15 IQ points and is the world's greatest single cause of preventable brain damage[8]. The possible effects of iodine deficiency are summarized in Table 1. According to the latest WHO report on global iodine status, iodine deficiency occurs in 47 countries worldwide (Australia has been shown as an iodine replete country in the global iodine deficiency status map based on median UIE levels-summarized in figure 2)[9]. However, in the Global Scorecard 2010 on iodine deficiency, Australia has been included as an iodine deficient country[10].

Table 1: Health consequences of iodine deficiency disorders (adopted from WHO/UNICEF/ ICCIDD, 2007[8])

Physiological groups	Health consequences of iodine deficiency
All ages	Goitre Hypothyroidism Increased susceptibility to nuclear radiation
Fetus	Spontaneous abortion Stillbirth Congenital anomalies Perinatal mortality
Neonate	Endemic cretinism including mental deficiency with a mixture of mutism, spastic diplegia, squint, hypothyroidism and short stature Infant mortality
Child and adolescent	Impaired mental function Delayed physical development Iodine-induced hyperthyroidism (IIH)
Adults	Impaired mental function Iodine-induced hyperthyroidism (IIH)

Methods for researching iodine deficiency

A variety of methods have been recommended by the WHO/UNICEF /ICCIDD for population iodine estimation. Many of these methods are costly and invasive while some are extremely cost effective. We have set out the brief summary of the methods in Table 2.

Table 2: Methods of monitoring population iodine status (adopted from WHO/UNICEF/ICCIDD, 2007[8])

Monitoring indicator (units)	Age group for assessment	Advantages	Disadvantages	Application
Median urinary iodine concentration (µg/L)	School age children and pregnant women	- Spot urine specimens are easy to obtain - The most practical biochemical marker for iodine nutrition, when carried out with appropriate technology and sampling - Feasible to process large numbers of samples at low cost - Cut-off points proposed for classifying iodine nutrition into different degrees of public health significance are well established - External quality control program in place	- Assesses iodine intake only over the past few days - Meticulous laboratory practice is required to avoid contamination with iodine - A sufficiently large number of samples must be collected to allow for varying degrees of subject hydration and other biological variations among individuals - Not suitable for individual assessment	- Median UIC among school children and adult population (≥ 6 yr) - <20 µg/L – severe iodine deficiency - 20-49 µg/L- moderate iodine deficiency - 50-99 µg/L- mild iodine deficiency - 100-199 µg/L- adequate iodine nutrition - 200-299 µg/L- above requirement - ≥300 µg/L- Excessive - Median UIC among pregnant women : - <150 µg/L – insufficient - 150-249 µg/L- Adequate iodine nutrition - 250-499 µg/L- above requirements - ≥500 µg/L- Excessive - For lactating and children <2 years of age median urinary iodine concentration >100 µg/L considered adequate iodine nutrition.
Goitre rate assessed by palpation (%)	School-age children	- Simple and rapid screening test - Requires no specialised equipment	- Specificity and sensitivity of palpation are low in grades 0 and 1 due to a high inter-observer variation - Responds slowly to changes in iodine intake	Degree of IDD by goiter rate : 0-4.9% - None, 5-19.9% - Mild, 20-29.9% - Moderate, ≥30% - Severe

Monitoring indicator (units)	**Age group for assessment**	**Advantages**	**Disadvantages**	**Application**
Goitre rate assessed by ultrasound (%)	School-age children	- A more precise measurement of thyroid volume compared with palpation - Safe, non-invasive - International reference values for thyroid volume in schoolchildren are available as a function of age, sex, and body surface area	- Expensive equipment and a source of electricity is needed - Operator needs to be specifically trained in the technique - Responds slowly to changes in iodine intake	Degree of IDD by goiter rate : 0-4.9% - None, 5-19.9% - Mild, 20-29.9% - Moderate, ≥30% - Severe
Thyroid Stimulating Hormone (mIU/L)	Newborns	-Measure thyroid function at a vulnerable age when iodine deficiency directly affects the developing brain - If screening programs to detect congenital hypothyroidism is in place then only additional cost will be for data analysis - Collection by heel stick and storage on filter paper is simple - Blood spots can be stored for several weeks at cool, dry room temperatures	- Not recommended to be set up solely to assess community iodine deficiency due to expense - Cannot be used when antiseptics containing iodine are used during delivery - Requires use of a standardized, sensitive assay - Should be taken either from the cord at delivery or by heel prick test at least 48 hours of birth to avoid physiological newborn surge	A <3% frequency of TSH values >5 mIU/L indicates iodine sufficiency in a population
Thyroglobulin (µg/L)	School-age children	- Collection by finger stick and storage on filter paper is simple - Can be stored for several weeks at cool, dry room temperatures, so sampling practical even in remote areas -Measures improving thyroid function within several months after iodine repletion - Standard reference material is now available, but needs to be validated -An international reference range has been established	- Expensive immunoassay - Requires laboratory infrastucture	Reference interval in iodine-sufficient children is 4-40 µg/L

Why should iodine deficiency be studied?

Australia has been recognised as an iodine deficient country since the early 1900s[11]. In mainland Australia some regions have been documented as being endemic goitre areas since 1933[12]. F.W. Clements, who was the first Director of the Nutrition Unit at the institute of Anatomy, Canberra, clearly identified these goitre prone areas, they included the Atherton Tablelands in Queensland; along the Great Dividing Range extending through New South Wales into Victoria, the Canberra region, the township of West Wyalong in New South Wales and the Gippsland region in Victoria[13]. In Tasmania IDD was widely recognised as a major public health problem and goitre monitoring and urinary iodine excretion testing have been in place there since 1949[14].

Several attempts have been made to deal with iodine deficiency in Australia since the middle of last century. In the late 1940s there was a national iodine tablet distribution program to school children and other vulnerable populations in the areas identified as goitre prone. The supplementation continued in some areas until the late 1960s. In 1953 in the Australian Capital Territory (ACT) and in 1966 in Tasmania iodine supplementation via bread products was also introduced. This program was discontinued in 1976 in Tasmania and in 1980s in the ACT, apparently, due to high rates of hyperthyroidism particularly in the elderly [13].

In the early 1990s a number of surveys conducted in Tasmania indicated that the population was iodine sufficient and the median urinary iodine concentration (MUIC) was above 200 µg/L[15]. Later, during 1998-2000 several cross sectional urinary iodine surveys among Tasmanian school children indicated mild iodine deficiency[16]. Similarly, studies in New South Wales in 1999[17] and in 2000[18]; and in Melbourne in 2001[19] also showed mild iodine deficiency among school children. In 2004 the National Iodine Nutrition Study (NINS) conducted urinary iodine studies on school children from five states in mainland Australia (New South Wales, South Australia, Victoria, Queensland and Western Australia). This study found that the Australian population overall was iodine deficient[20]. The Australian Capital Territory, Northern Territory and Tasmania were not included in this study. In New South Wales (MUIC 89.0 µg/L) and Victoria (MUIC 73.5 µg/L) children were found to be mildly iodine deficient and South Australia had borderline optimal iodine status (MUIC 101.0 µg/L). Queensland (MUIC 136.5

µg/L) and Western Australian children (MUIC 142.5 µg/L) were found to be iodine replete. Among all the surveyed states the median UIC of Victorian school children was the lowest. However, the total sample of the NINS was not nationally representative[11].

Urinary iodine studies conducted on pregnant women in Australia are mainly limited to New South Wales, Victoria and Tasmania[17,21-27]. All these studies showed deficiency among this vulnerable population group and the median UIC ranged from 47-104 µg/L. These levels are below the cut-off value for iodine deficiency during pregnancy (≥150 µg/L).

As we have seen Gippsland had a reputation as an iodine deficient area and participated in the national iodine tablet supplementation program for school children[28,29].An in depth review of the relevant literature indicates that the last iodine status survey in Gippsland was Clements 1948 study. For this study he used the thyroid palpation method for measuring the incidence of goitre[30]. The NINS team were planning to collect urine samples from the Gippsland region, but this did not occur (Personal communication with Dr. Mu Li on 9 May 2006). Despite Gipplsand being a goitre prone area and despite WHO recommendations that iodine status should be monitored every 5 years and that areas of high risk required separate monitoring testing was not done[8]. Therefore the actual iodine status of the Gippsland population, prior to this thesis, was unknown. Clearly there was a major imperative to undertake an iodine monitoring program in Gippsland.

From the NINS data it was obvious to the scientific community that iodine deficiency had re-emerged as a national problem. Iodine deficiency now in the twenty first century was recognised at the national level as a major public health nutrition problem across Australia. In response to this problem, Food Standard Australia and New Zealand (FSANZ) introduced a national iodine supplementation program via bread products from October 2009. Evidence from a regular surveillance program for monitoring population iodine status in Tasmania in use since 1949 supported supplementation to maintain the population iodine status at an acceptable level. For example, Tasmanian school children were found to be mildly iodine deficient during 1998-2000 by several cross sectional urine studies[16]. The local health authority responded to this and started a bread fortification program. This seems to have had positive results as a study conducted in 2001 found that Tasmanian school children had close to optimal iodine status[25].

However while the monitoring and supplementation via bread has worked for school children it has not worked for pregnant women due to the much greater requirement for iodine during pregnancy and breast feeding[25].

Despite having a similar iodine deficiency history as Tasmania, there has been no recognition at the national level of iodine deficiency as a problem for the Gippsland region. The issue of iodine deficiency in Gippsland seems to have been forgotten by most people, except those people who remember taking iodine tablets as school children.

Importance of regional and subregional studies

As the Australian history shows iodine deficiency is a regional and sub regional issue as well as a national one. Lack of iodine in the soil is the main cause of regional dietary iodine deficiency as the water and agricultural products grown in these areas lack iodine. As discussed above, certain geographical areas and regions in Australia were known as endemic goitre areas[13]. This is also common in other parts of the world. For example, endemic goitre is common in the Xinjiang province of China[31] and Derbyshire region in the UK [32]. In addition, there may be very localized sub regional variation in the iodine status of a population due to close occurring geological difference. A Danish study found sub regional difference in population iodine status[33]. There were high concentration of water iodine in Skagen (140 µg/L) where the aquifer source rock contained marine deposits, this was in contrast to Randers (2 µg/L) (both towns are situated in the Peninsula of Juteland in Denmark and the distance between the two towns is 143.54 kilometres; the distance was calculated by Google maps distance calculator) which had a different type of rock (Andersen et al., 2008). The study found higher urinary iodine concentrations in Skagen and suggested that the significant difference in the population urinary iodine concentration between those two areas were due to differences in the iodine content of the water. It is vital to address the regional and sub regional variation in iodine deficiency as the estimated total dietary intake of iodine from local food and water may be lower than the average national estimation. And applying a national strategy to prevent iodine deficiency may result in suboptimal iodine supplementation in deficient regions. Clearly the belief that globalised or nationalized food distribution networks has removed regional and sub regional differences needs to be questioned. Alternatively much of the global and national food supply may be sourced from iodine deficient locations.

Gippsland: what sort of studies were needed and justification for a way forward via regional studies

Anecdotal evidence was available that raised the question about Gippsland returning to iodine deficiency. Therefore Gippsland researchers were keen to support a study that aimed to look at the iodine status of the Gippsland population. WHO/UNICEF/ ICCIDD guidelines supports Urinary Iodine Excretion testing among school children and other population groups, such as pregnant women, as the gold standard to measure population iodine status. However, as urine tests are intrusive and relatively expensive, we planned to use a variety of surrogate markers to estimate the iodine status of the Gippsland population before moving to conduct urinary analysis. There was divided opinion on this matter with some experts in support of our proving our concept before moving to intrusive and expensive testing while others advised us to proceed directly to national advocacy to address iodine deficiency in Gippsland. We considered that our advocacy would be more powerful if we had some evidence of iodine deficiency in the Gippsland region.

Therefore we formulated a three stage research plan to find the most suitable methods to get the evidence to prove or disprove our hypothesis.

Stage 1: Literature review and hypothesis development

At this stage of the thesis research a detailed literature review was done using the internet and manual searching of relevant literature using specific key words and dates. In addition, several visits were made to the National Archives in Canberra and Melbourne and the Victorian Public Record Office. Later, we issued a press release in the Gippsland region's print and electronic media to seek evidence about the community memory in relation to taking iodine tablets in Gippsland schools during late 1940s to late 1960s. All this information helped us to develop our hypothesis.

Stage 2: Establishing surrogate markers for environmental and population iodine deficiency

Environmental surrogate markers

Soil analysis to measure iodine concentrations would be the best method for establishing the level of environmental iodine deficiency in the Gippsland region. However, soil analysis is expensive, time consuming and requires advanced laboratory facilities. On the other hand testing for water iodine concentrations provides a reliable environmental surrogate marker. Testing water is relatively inexpensive and it is able to be quickly analysed using simple laboratory facilities. So we decided to research the water iodine concentrations in Gippsland regional water supplies. We also considered testing milk to correlate milk and milk products iodine concentrations with the regional water iodine concentrations. However, testing milk iodine concentrations is expensive and we were not successful in obtaining a grant for this proposed research. Therefore we did not research milk iodine concentrations in the Gippsland region.

Population Surrogate markers

We wanted to look for evidence of any increasing number of cases of hypothyroidism in Gippsland as this would seem to be a logical consequence of returning iodine deficiency. Iodine deficiency could result in increased hypothyroidism in the general population. There was some anecdotal evidence of an increasing number of cases of hypothyroidism among the adult population in the Gippsland region. To try to research the incidence of hypothyroidism in Gippsland, we applied to collect thyroid function test results (mainly T3, T4 and TSH) from a key Gippsland pathology group for the 10 years, from 1996 to 2006. We were successful in gaining access to this database but the data it contained was not of a suitable standard to analyse. Despite a great deal of preliminary analysis it was decided by the researchers and the pathology service that the data were not reliable. Following this failure we also attempted to get information from the Healthcare Insurance Commission (HIC) about the number of patients taking thyroid hormone supplement medications over the last decade but this also proved difficult.

We then looked for an alternative surrogate marker for population iodine status. Neonatal Thyroid Stimulating Hormone (TSH) is an important emerging surrogate marker for monitoring population iodine status[8]. While WHO supports the advantages of this method, there has been some doubt about its value due to some factors that could influence the TSH levels[34]. Considering the size and quality of the studies in support of the use of TSH level as a iodine monitoring tool we considered that it could be a feasible option for assessing population iodine status in Victoria[35]. In Victoria, heel prick blood samples are collected from newborns at 2 or 3 days of age and immunoassay technique is used to analyse the blood samples[39]. In Victoria more than 99.4% of neonates in 2002 have a newborn screening test. Neonatal TSH levels have been analysed at the Victorian Clinical Genetics Laboratory (VCGS) since 1977. We concluded that a retrospective neonatal TSH database analysis of the heel prick samples collected by the VCGS would be a good option to provide a surrogate marker of Gippsland iodine status. When the study was being conceptualized it was considered sensible to analyse all the Victorian data.

Stage 3: Direct measurement of population iodine deficiency

As discussed above the measurement of urinary iodine concentrations is considered as the gold standard for population iodine status measurement. The neonatal TSH marker is, arguably an excellent indication of iodine deficiency in the last trimester of pregnancy. This suggested to us that a urinary iodine study of a cohort of Gippsland pregnant women would be a valuable addition to our study. Pregnant women have the most need for iodine and are prone to iodine deficiency due to increased requirement of iodine during pregnancy and dietary recommendations regarding the limitations of intake of eggs, fish and salt. Our assumption was after obtaining preliminary evidence of iodine deficiency in Gippsland at stage 1 and 2; we would be in a position to get permission from public hospitals and private clinics across Gippsland to obtain urine samples from pregnant women. We also planned to collect information on pregnant women's diet,supplementation regimes and knowledge about iodine using a short self administered questionnaire. To support this expensive part of our study, we applied for and received a small strategic grant from the Monash University Faculty of Medicine, Nursing and Health Sciences.

We also considered collecting urine samples from Gippsland school children . However, due to limited time and lack of funding we did not proceed with that research option.

Hypothesis formation

The information about iodine deficiency in Gippsland prior to our study was dated and incomplete. As the Gippsland region was not included in the NINS study it is difficult to say whether the iodine status in Gippsland was better or worse than Victoria as a whole. Furthermore the NINS study was conducted in 2003-2004 and as a result it has less validity in helping us gain an accurate picture of the current iodine status of Victoria. In accordance with WHO protocols even if NINS had collected data in Gippsland it would have been time to repeat this study (or a similar study) in 2009. Therefore we considered that our study should look at the historical and contemporary iodine status of the Gippsland population so we decided on the following hypothesis:

Hypothesis

There is a recurrence of dietary iodine deficiency in the Gippsland region.

1. Building our case

This study had three main objectives.

- To examine the historical evidence of dietary iodine deficiency.
  Gippsland has been known as an iodine deficient region since early 1900s. Contemporary publications on iodine deficiency in Australia lack detailed evidence of iodine deficiency in this region. So we wanted to find what historical evidence was available.
  Part 1: Search for historical evidence of iodine deficiency using archival research, rare book and journal collection searches and asking for Gippsland people to remember previous iodine supplementation programs they had participated in.
  The historical evidence pointed to the likelihood of environmental iodine deficiency in Gippsland.
- To research environmental iodine status.
  Places with a historical evidence of dietary iodine deficiency are commonly associated with environmental iodine deficiency. Generally, iodine deficiency is associated with a lack of iodine in the soil and as a result food products

grown in the iodine deficient region contain low amount of iodine. Soil can be directly tested to measure the iodine concentration but this is expensive and time consuming. Water is a good surrogate marker for environmental iodine deficiency. We could not find any historical or contemporary data on soil or water iodine concentrations in the Gippsland region. As the second part of our study we tested water iodine concentrations across Gippsland.

Part 2: Research for environmental evidence of iodine deficiency by measuring the iodine concentration of drinking water from 18 water treatment plants and rain water tanks across central, west and south Gippsland.

- To estimate the population iodine status and factors affecting it.

Theories about changing diet suggest that differences in environmental iodine are smoothed out by the diversity of sources for modern diets. Therefore the next step in testing our hypothesis involved if there is any regional difference in the population iodine status in Victoria. From every newborn baby in Australia blood is collected after birth and among other biochemical component blood Thyroid Stimulating Hormone (TSH) level is measured which can be used as population iodine monitoring tool. This is recognised iodine monitoring tool which can be used effectively and economically monitoring population iodine status. So we wanted to find look at the population iodine status through part 3 of our study.

Part 3: Victorian (including Gippsland) Neonatal population iodine status estimation by retrospective neonatal Thyroid Stimulating Hormone (TSH) data analysis from 2001 to 2006.

The result from the neonatal TSH methodology concludes the emerging iodine deficiency in Gippsland as well as in Victoria and a call for urine iodine testing with pregnant women. In addition , there was no relevant information on the pregnant women's intake of iodine rich food and supplementation consumption. So we wanted sought these answers through part 4 of our study. One of the major advantages of this part of our study was its timing. Initially our plan was to collect the urine samples prior to the fortification of bread. But, we found that the urine sample collection from pregnant women took more time than we expected. Therefore the urine sample collection time span covered more than a year which provided us with the opportunity to look at the efficacy of the bread fortification program.

Part 4: Gippsland pregnant women iodine status estimated by urinary iodine concentration measurement and an exploration of factors influencing iodine status during pregnancy by application of a self-reported food and supplementation questionnaire.

Chapter plan

This is a thesis by publication where most of the chapters are published, in press or submitted journal articles. The thesis is divided into seven chapters as follws:

1. Chapter 1: Introduction: This chapter sets the scene for the whole study. It includes an overview of dietary iodine deficiency and common methods to monitor it. Then it looks at iodine status worldwide and then focuses on Australia, Victoria and Gippsland. The rationale for iodine studies in Gippsland are considered and the likely sub studies that could support the development of the hypothesis and research objectives are discussed. This chapter concludes with a description of the four sub-studies used in this thesis.

2. Chapter 2: Methods: This chapter provides an overview of the different methods that had been applied in this study. The discussion includes the place of study, establishment of the study, data collection activities and how quality was maintained throughout the study.

3. Chapter 3: Paper 1: 'Taking a history: The learnings that national food science forgot'. This paper reviews the historical evidence of iodine deficiency in the Gippsland region. In some contemporary documents on iodine deficiency in Australia, Gippsland has been included as a region with a history of endemic goitre. However, in recently published reports we did not find any evidence that the history of iodine deficiency and supplementation in the Gippsland region had been considered. The areas commonly mentioned in national publications were Tasmania and Australian Capital Territory (ACT). This paper describes the evidence of endemic goitre and the existence of an iodine tablet distribution program in Gippsland. It concludes that national iodine supplementation policies need to be aware of history and of regional diversity. Though this paper is presented as the first

chapter it was the final chapter to be written as data collection was continued right through till the last stage of candidature. There is still much work to be done in writing the history of iodine and iodine deficiency in Gippsland.

4. Chapter 4: Paper 2: ‘Is Gippsland environmentally iodine deficient? Water iodine concentrations in the Gippsland region of Victoria, Australia’. This paper addresses the evidence of environmental iodine deficiency in the Gippsland region. We are not aware of any previous study that looked in detail at the environmental iodine status of the Gippsland region. We chose water as a surrogate marker for our study and collected water samples from water treatment plants and rain water tanks across central, west and south Gippsland. This paper also explores the daily iodine contribution people would receive from drinking this Gippsland water and considered any possible relationship between iodine concentration in the water and distance from the sea.

5. Chapter 5: Paper 3: ‘Increased iodine deficiency in Victoria, Australia: Analysis of neonatal TSH data 2001 to 2006’. This paper sets out to plot the Victorian population iodine status by analysis of neonatal Thyroid Stimulation Hormone (TSH) data from 368,552 cases. Blood samples are regularly collected from all the newborn babies in Victoria and TSH levels are measured for congenital hypothyroidism by the Victorian Clinical Genetics Services (VCGS). According to WHO/ UNICEF/ ICCIDD criteria, >3% of the newborns having >5 mIU/L of blood TSH level is indicative of population iodine deficiency. The paper shows a worrying increase in iodine deficiency among the newborn population. This method is a novel, cost effective and easy method of monitoring population iodine status from the level of Victoria as a whole right down to the level of local hospitals. Done regularly in each state and territory it could be used to monitor the effectiveness and need for iodine fortification programs.

6. Chapter 6: Paper 4: ‘Urinary iodine deficiency in Gippsland pregnant women. The failure of bread fortification’. Urinary iodine level measurement and analysis is considered as the gold standard for monitoring population iodine levels. Paper 4 reports on a urinary

iodine study of 86 Gippsland pregnant women. This paper also provides information on the women's diet, supplementation regimes and knowledge of iodine. Data collection for this part of the study overlapped the initiation of the national iodine supplementation study via bread products and this enabled us to compare the urinary iodine levels between pre fortification and the fortified periods.

7. Chapter 7: Integrated discussion: In this chapter the findings of this four part study are analysed in relationship to our hypothesis and objectives. The strength and contribution of this thesis to local, national and international knowledge on iodine deficiency are discussed. In addition, this chapter mentions some limitations of the study and suggests some key future research.

CHAPTER 2

Methods

This study has used multiple methods to collect information to test the hypothesis that there is a recurrence of dietary iodine deficiency in the Gippsland region. The methods ranged from archival data collection and research to bench science. As the methods are very different from each other this chapter provides an overview of the methods that we applied in each of the four sub studies. A more detailed and specific methods section is contained in each of the four papers.

Part 1:

Search for historical evidence of iodine deficiency using archival research, rare book and journal collection searches and asking Gippsland people to remember previous iodine supplementation programs they participated in.

The Settings

The information for this research was collected from the following locations:

- Victorian Public Records Office
- National Archives, Melbourne and Canberra
- Monash University Libraries , Rare Books Collection section
- Internet: using search engines like Google and also specific key words
- Community settings, in the Gippsland region

Establishing the Study

Initial information was obtained from archival research and internet sources. Later, we devised a press release that was distributed by the Monash University Gipplsand Campus media department. The press release urged anyone who has taken iodine supplement tablets in school during the period 1948-1965 contact Ashequr Rahman. Following that media release, there were three media interviews: a live radio interview with ABC Gippsland, a TV interview with Win TV and a newspaper interview with the Latrobe Valley Express. Following the interviews, there were responses from 17 people saying that they had taken iodine tablets during the period 1950-1965 while studying in different schools in the Gippsland region.

Data Collection Activities

Archival information was collected by physical visits to the Victorian Public Record Office and the National Archives in Melbourne and Canberra. For the community memory study, the responders contacted us via email, mail and telephone. Commonly, the responders gave the name of their school and the time period they took the iodine tablets. Relevant information from the archive and rare books were also photocopied or a digital version was obtained.

Data analysis

The information from the respondents were inserted in Microsoft Excel Spreadsheet. Epi-Info Version 3.2.1 (CDC Atlanta, USA) was used as a mapping software tool.

Ensuring Rigour

Several visits were made to the Archives and Public Record Office to find evidence of iodine deficiency in the Gippsland region. Library and museum websites across Australia were browsed electronically for relevant journals and rare books and when relevant information was found it was collected or read in situ.

Part 2:

Research for environmental evidence of iodine deficiency by measuring the iodine concentration of drinking water from 18 water treatment plants and rain water tanks across central, west and south Gippsland.

The Setting

Eighteen water treatment plants from central, west and South Gippsland operated by Gippsland Water and Westernport Water.

Establishing the Study

Ethics committee approval: An amendment was made to the Monash University Standing Committee on Ethics in research involving Humans (SCREH) on 29/11/07 to test the water iodine concentration. The details of the original ethics approval is:

Project number: 2007001742-CF07/2818

Title of the project: Incidence of thyroid dysfunction in Gippsland due to iodine insufficiency

Original approval date: 10 September 2007

Sampling: The total number of water treatment plants Gippsland Water and Westernport Water use is 18 and and water from all sites were included in the study. Both untreated and treated water were collected from the water treatment plants with the assistance of employees of Gippsland Water and Westernport Water. Water coming out of the water purification plant that goes into the tap water system was termed 'treated water' and the raw water going into the water purification plant was termed 'untreated water'. Four rain tank water samples were also collected from different geographical locations in Gippsland.

The water samples were tested by AR under the supervision of Dr. Barbara Panther at the Environmental Laboratory of the School of Applied Science and Engineering, Monash University Gippsland Campus.

Laboratory technique: Sandell-Kolthoff catalytic reduction method is a recommended method for measurement of low concentrations (<80 µg/L) of iodine in drinking water[36]. In this method, water samples are digested in hydrochloric acid and cerium (IV) and arsenic are added. If iodine is present in the sample, arsenic is oxidised and become As^{5+} and ceric cations are reduced and converted to Ce^{3+}. This reaction causes a colour change reaction from yellow to clear solution and this can be detected by using a Vis Spectrophotometer.

Ensuring Rigour

Laboratory quality control regulations and occupational health and safety Rules were followed.

Water samples were preserved in -20° C prior to analysis. All the water samples were analysed twice and the spectrophometer was calibrated using standard control samples.

Data analysis

The water iodine concentration data was entered into Microsoft Excel spreadsheets and then analysed using SAS Enterprise Guide 4.1(SAS Inc., USA). ARC GIS 9.3 (ESRI, USA) was used as a mapping software.

Part 3:

Victorian (including Gippsland) Neonatal population iodine status estimation by retrospective neonatal Thyroid Stimulating Hormone (TSH) data analysis from 2001 to 2006.

The Setting

Victorian Clinical Genetics Services (VCGS), Royal Children's Hospital, Melbourne.

Establishing the Study

Ethics committee approval

- Ethics approval was obtained from the Royal Children's Hospital Human Research Ethics Committee. The details of the ethics approval is:

  HREC reference number: 28096 A

  Project Title: Iodine insufficiency among newborns in Gippsland region.

  Date of original approval: 20 November 2008

- An amendment was also made to the Monash University Human Research Ethics Committee on 23/02/10. The details of the original ethics approval is:

  Project number: 2007001742-CF07/2818

  Title of the project: Incidence of thyroid dysfunction in Gippsland due to iodine insufficiency

  Original approval date: 10 September 2007

Sampling

All the newborn babies born in Victoria between 2001 and 2006 who provided heel prick blood samples were included in our sampling frame. Valid information was available for over 368, 323 newborns which represents >95% of the babies born during that timeframe. The repeat blood samples and blood samples taken before 2 days and after 4 days of birth were excluded from the analysis.

Recruitment and consent

All the information was de-identified (all names, addresses and hospital admission numbers had been deleted) so there was no requirement of obtaining consent from the parents.

Data Collection Activities

Database development

The data was extracted from the Victorian National database (originally stored in a Microsoft Server format) and then the data was converted to a format suitable for SAS software. SAS Enterprise Guide 4.1 was used for the statistical analysis.

Laboratory technique

The tests were performed in the normal manner over the years at the VCGS. Strict quality control was used and the international guidelines for the analysis of the blood samples for TSH were followed. The important features of the quality control were:

1. The use of one source of TSH calibrators and reagents over the period of the analysis by one laboratory covering the whole population of Victoria.

2. The Centers for Disease Control in the United States of America provided external quality assurance. This ensured that the results were in agreement with other laboratories thus minimizing bias. The CV range over the period was 10% to 20% (average 15%).

3. The TSH assays were all carried out with reagents from BIOCLONE Australia. The TSH kit used is Elegance neonatal TSH ELISA kit (In use since 1993). The instrument used was a LabSystems Multiskan RC plate reader. These are both well regarded and appropriate products.

Ensuring Rigour

Data analysis

The WHO/ UNICEF/ ICCIDD criteria was followed. According to this WHO epidemiological criteria, having a neonatal TSH above 5 mIU/L blood in less than 3% of neonates indicates an iodine replete population, a frequency of 3-19.9% indicates mild iodine deficiency and frequencies of 20-39.9% and above 40% indicate moderate to severe iodine deficiency[8].

Tests of significance (Chi Square) were performed while doing the statistical analysis.

Part 4:

Gippsland pregnant women iodine status estimation by urinary iodine concentration measurement and an exploration of the dietary and iodine supplementation factors influencing iodine status during pregnancy via a self-reported questionnaire.

The Setting

Seven hospitals and clinics across Gippsland.

Establishing the Study

The ethics approval was obtained from Human research Ethics Committees of Monash University, Latrobe Regional Hospital and West Gippsland Health Care Group and permission was obtained from all other participating hospitals and clinics.

- The details of ethics approval from the Monash University Standing Committee on Ethics in Research Involving Humans (SCERH) is:

  Project number: CF08/2196-2008001063

  Title of the project: Dietary iodine insufficiency among pregnant women in the Gippsland region

  Approval date: 18 September 2008

- The details of ethics approval from the Latrobe Regional Hospital Research Ethics Committee is:

  LRH HREC Reference Number: 2008-14

  Title of the project: Dietary iodine insufficiency among pregnant women in the Gippsland region

  Approval date: 13 February 2009

- The details of ethics approval from the West Gippsland Healthcare Group is:

  Project Reference Number: not mentioned

  Title of the project: Dietary iodine insufficiency among pregnant women in the Gippsland region

  Approval date: 25 April 2009

Sampling

By following the standard sample calculation equation it was found that 86 urine samples from pregnant women were required for this study[37]. The formula used for the sample size calculation was:

$n = (Z \times CV\%D)^2$ where the Confidence Interval (Z) for 90% was 1.64; CV% (variance square root divided by mean, as a percentage) at the population level was 56.4; D (the precision range) was ±10%.

Sample collection: From Anti-natal Clinics at hospitals and clinics in the Gippsland region. These were:

Hospital/ clinic	**City/Shire**
Latrobe Regional Hospital	Latrobe City
Warragul Hospital	Baw Baw Shire
Macleod Street Medical centre, Bairnsdale	East Gippsland Shire
Leongatha Hospital	South Gippsland Shire
Leongatha Medical Group	South Gippsland Shire
Sale Hospital	Wellington Shire
Wonthaggi Hospital	Bass Coast Shire

Recruitment and consent

The pregnant women were asked to participate in the study by AR and were then given the sample collection kits (including self administered short dietary questionnaire). Consent was obtained prior to sample collection.

Data Collection Activities

Urine samples collection

The participants were asked to bring a morning urine sample when attending their next ante-natal class or visit. In some cases, some spot urine samples were requested to ensure the target number of samples were reached.

Questionnaire

A short dietary questionnaire was used to find the iodine rich food intake pattern of these women during their pregnancies.

Laboratory technique

The urine samples were analysed at the laboratory at Westmead Hospital, Sydney by using Sandell-Kolthoff catalytic reduction method. This is a reference laboratory accredited by the International Centre for Control of Iodine Deficiency Disorders (ICCIDD) for the Asia-Pacific region for measuring urinary Iodine concentration.

Ensuring Rigour

Data analysis

The data was entered in Microsoft Access and analysed by using SAS Enterprise Guide 4.1. Data entry was checked for possible data entry errors. ARC GIS 9.3 (ESRI, USA) was used as a mapping software.

Quality control issues

The Urine samples were collected and preserved by maintaining a proper cold chain. The samples were immediately stored in an ice box after collection from the participants and then preserved in a -20^{o}C freezer in the School of Applied Science and Engineering at Monash University

Gippsland Campus. Later the samples were transferred by a medical courier service to Sydney Westmead Hospital maintaining proper temperature control thorough out.

Conclusion

The four sub studies resulted in four published papers. This chapter has presented an overview that demonstrates the way in which the separate studies build to provide strong evidence in support of the hypothesis. Each paper chapter presents the methods used in more detail. In the linking page the name of the following paper, details of the publication status and a preface narrates how each chapter build and links together.

CHAPTER 3

Paper 1

Taking a history: The learnings that national health science forgot

Journal: The Australian Journal of Rural Health

Status: Under review (9th of August 2010)

Preface

This paper reviews the historical evidence of dietary iodine deficiency in the Gippsland region and sets the scene for the entire study. It addresses the forgotten issue of iodine deficiency in Gippsland and concludes with a recommendation of further study in this area. In addition, it recommends moving beyond a national approach to consider regional and sub-regional differences. The consideration of regional diversity is vital to the formulation of an effective iodine supplementation policy.

Part B: Declaration for Thesis Chapter

PART B: Suggested Declaration for Thesis Paper 1

Monash University

Declaration for Thesis Paper 1

Declaration by candidate

In the case of Paper 1 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, establishment of research database, writing and editing of the paper	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Assoc. Prof Janice Chesters	Study design, writing and editing of the paper	N/A
Dr. Gayle Savige	Study design, writing and editing of the paper	N/A
Dr. Nicholas Deacon	Study design, writing and editing of the paper	N/A

Candidate's Signature		Date
	[redacted]	4/08/2010

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Monash University Department of Rural and Indigenous Health, 3 Ollerton Avenue, Moe, VIC-3825

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

	Co-Authors Signatures	Date
Signature 1	[redacted]	4/08/2010
Signature 2	[redacted]	4/08/2010
Signature 3	[redacted]	4/08/2010

Manuscript Title: Taking a history: The learnings that national health science forgot

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Abstract

Objective: This paper provides evidence for the importance of taking an effective history and considering regional differences before formulating national health policies.

Design: Qualitative study; the data collection technique included manual searches of rare book collections, a search of the Victorian Public Record Office and Australian Archives files and a local media appeal for information about iodine and iodine supplementation in Gippsland and other regions of Australia.

Setting: Regional Victoria and Australia as a whole.

Participants: A total of 17 community members from the Gippsland region provided information on taking iodine tablets between the late 1940s and the late 1960s.

Main outcome measures: Information from the community members who took iodine tablets, archival material, published articles in journals on iodine deficiency disorder (IDD) in Gippsland, government reports and meeting minutes regarding distribution of iodine supplementation in Gippsland.

Results: Taking an effective history is vital to planning national health interventions. It may not be adequate to just search electronic data bases. A thorough search of archival and hard copy material and consultation with members of the population can help find key historical data that can inform better health policy action.

Conclusion: There is strong historical evidence of dietary iodine deficiency in the Gippsland region and in a number of other regions across Australia. Government and health authorities should undertake regular iodine status monitoring in these regions. Considering regional difference is important when making national health policy.

Key words:

Iodine tablets, endemic goitre, iodine deficiency disorder, Gippsland, Victoria

What this paper adds

1. **What is already known on this subject**

   - Dietary iodine deficiency is regarded as most preventable cause of brain damage in newborns worldwide and Australia as a whole is an iodine deficient country.
   - There has been a history of iodine deficiency in Gippsland region of Victoria, Australia.

2. **What this study adds**

- There is a strong historical evidence of iodine deficiency disorder in Gippsland and iodine tablet were distributed among school children from late 1940s to late 1960s.
- Government and health authorities should undertake regular iodine status monitoring of the Gippsland population.
- Regional iodine deficiency is important while formulating a national iodine fortification program.

Introduction

Australia as a whole is classified by the World Health Organisation (WHO) as a mildly iodine deficient country[1]. The WHO recognises even mild iodine deficiency as the most common preventable cause of brain damage in newborns. In Australia an effective supplementation program is needed to prevent the damage that iodine deficiency can cause. Food Standards of Australia and New Zealand (FSANZ) introduced a mandatory national bread fortification program in October 2009. The uniform national focus, the vehicle used in the fortification program and the levels of fortification recommended were calculated using dietary modelling data from the most recent National Nutrition Survey (NNS), undertaken in 1995[2]. We argue that FSANZ in using the National Nutrition Survey (NNS) has overlooked regional and sub regional diversity and the importance of taking a good history and learning from it[3].

The WHO recommends that iodine levels in iodine deficient countries be monitored every five years and that the monitoring in regions or areas of risk should be carried out separately from national studies[4]. FSANZ has not monitored iodine levels nationally or conducted the WHO recommended separate monitoring in areas with a history of iodine deficiency like Gippsland, Victoria. Evidence from Tasmania suggests that bread supplementation does not reduce iodine deficiency in the population group most in need of it - pregnant and breast feeding women and their young babies[5]. Good historical data augmented by up to date studies suggests that the national bread fortification program will not be successful in its current form.

This paper reviews the historical and contemporary evidence of iodine deficiency and supplementation in Australia and the Gippsland region of Victoria in particular. The results of ignoring the history of the regional and sub regional differences in iodine deficiency and the evidence on supplementation may result in the mistakes of the past being repeated to the detriment of pregnant and breast feeding women and their young babies.

Methods

A systematic search for research papers was carried out electronically using key words (iodine deficiency, Victoria, Gippsland, iodine tablet distribution, endemic goitre, school health, goitre monitoring, iodine supplementation, nodular non toxic goitre) and key dates (1947, 1948, 1960, 1965, and 1975). The major health databases such as Pubmed, Medline, the Cochrane database and Google (including Google Scholar) were searched.

The database of the Victorian Public Record Office, and the National Archive, were also searched and produced the most valuable results. A manual search of rare book collections was also made.

Qualitative analysis was carried out on the text based findings. Other data were entered onto Microsoft Excel spreadsheets and digitally mapped using EPI Info (Version 3.4.1).

Results

Australia as a whole and Gippsland in particular had been identified as iodine deficient since the early 20th century[6]. Dr FW Clements, in a paper published in 1948, referred to the historical evidence of goitre in Gippsland that appeared in a school health report published by the Victorian Education Department in 1911[7]. In 1913-15, goitre was said to be common among high schools in girls in Leongatha, Bairnsdale, Sale and Warragul[6]. In 1923, 50% of the women teachers and 25% of high school girls from Bairnsdale schools were found to have goitres and 'iodine of sodium' (sodium iodide) was given as a prophylactic dose to prevent goitre[6].

Figure 3: A Gippsland family showing signs of endemic goitre in five out of seven family members. C. 1935.

Photo Courtesy: Monash University ARROW repository, Monash University: http://arrow.monash.edu.au/hdl/1959.1/4372

In 1948, Clements researched the clinical evidence of goitre among school

children from a Gippsland farming population[7]. In that study the incidence of goitre was found to be high. The goitre rate among girls was 54% and boys 41%[7]. In a monograph published by the World Health Organization in 1960 Gippsland was described as the 'home of goitre' in Victoria and the locations and incidence of goitre among Gippsland adolescents was documented[8]. Sutton also identified a high incidence of goitre in Gippsland[9].

In response to Clements studies showing high incidence of goitre among school children in Canberra in 1947, N.E. McKenna, Minister for Health, announced in a Federal Cabinet meeting held on 2nd August 1948 that the government would approve the free supply of iodine tablets to all the goitrous areas of Australia[10]. An attachment in that agenda showed the main goitrous areas in Australia, which included Gippsland[11]. On 19 August 1948 Prime Minister JB Chifley in a letter to all premiers advised that Commonwealth would supply a 10 mg tablet weekly for children, expecting and nursing mother to prevent goitre[12].

Richards, a medical historian has described the iodine tablet distribution program for Tasmania[12]. As the supplementation program for the whole of Australia was centralised we have assumed that the program was similar in Gippsland. The Commonwealth Health Department provided funding for the tablets which were supplied by Drug Houses of Australia and distributed to health departments, schools and the general public. The most common distribution method was for school teachers to designate a student as ‘goitre monitor’ who then handed out the tablets to every child in the class. The dosage of the tablets was 10mg of potassium iodide and students were advised to take one tablet a week[10].Iodine (potassium iodide) tablet supplementation started in the Gippsland region in 1948 or 1949. The program continued until the late 1960s. Cessation dates varied as local authorities seemed to continue with the program until the supply of tablets ran out.

The reasons for stopping the iodine tablet distribution in Gippsland region is unknown. Survey findings might have shown the population to be iodine replete or that iodine tablet supplementation was not helping in solving the iodine deficiency. However, we have been unable to find any evidence that such survey data exists.

H B Gibson, a Senior School Medical Officer in Tasmania involved in the Iodine prophylaxis and goitre monitoring, suggested that the iodine tablet supplementation program had failed to work in Tasmania[13]. In 1965, after 16 years of supplementation using iodine tablets Gibson suggested that it failed to prevent goitre at an 'acceptable rate' among adolescent girls in several regions of Tasmania. This resulted in a change to iodine supplementation via bread[13]. Surprisingly, iodine tablets were replaced by supplementation via bread in Tasmania and the ACT but to our knowledge, not in Gippsland. Recent studies have shown urine iodine levels close to the recommended levels in Tasmanian school children by 2001[4]. Unfortunately, the strategy applied in Tasmanian has not worked for pregnant women due to the much greater requirement for iodine during pregnancy and breast feeding.

Table 3: History of iodine intervention in Australia

(according to report prepared for the Australian Population Health Development Principal Committee of the Australian Health Ministers Advisory Committee, December 2007[14]). The information for 1948 and 2009 has been added to show the latest information.

Years	Intervention	Area
1920	Introduction of iodised table salt	Australia
1947	Iodine tablets provided to school children and pregnant and lactating women	ACT and Tasmania
1948	Iodine tablets provided to school children and pregnant and lactating women	Victoria (including Gippsland)
1953	Iodine containing bread improvers	ACT only
1966	Iodine containing bread improvers	Tasmania
1976	Discontinued use of iodine containing bread improvers due to high rates of Iodine induced hyperthyroidism	
2001	Voluntary use of iodised salt by the bread industry	Tasmania only
2009	Mandatory use of iodised salt by the bread industry	Australia

Accessing the community memory on iodine

As we had failed to find a full explanation of the iodine supplementation program in the Gipplsand context in the public record we decided to consult the local population. A press release was distributed by Monash University media department in 2007 asking that anyone who took iodine supplement tablets in Gippsland between the late 1940's and the early 1960's contact AR. There were responses from 17 community members saying that they had taken iodine tablets during the period of 1950-1968 while studying in different schools in Gippsland. Most of the respondents were female (70%) and all respondents had taken iodine tablets except for one respondent who reported taking the liquid form of iodine (Lugols Iodine). A typical response to our informal survey came from Mrs. M:

'In our childhood we took iodine tablets regularly. Our father was always conscious about this and used to buy iodised salt for us. My father is now 93 years old, lives in a nursing home and always gives emphasis to us buying iodised salt for him. Otherwise, he thinks he will become iodine deficient.'

The distribution of survey results is contained in Figure 4.

Figure 4: Distribution of respondents from the Gippsland region with history of taking iodine tablet

Discussion

The current mandatory national iodine fortification strategy was based on dietary modelling from the last National Nutrition Study (NNS) data, which was conducted in 1995[2]. The NNS estimated that average individual dietary intake of iodine at the population level is 100µg/day. It was estimated that bread fortification would add 43µg iodine/day and would increase the daily intake of iodine to 143µg/day. FSANZ commented that there was no obvious regional difference in the iodine concentration from food and beverages obtained in the NNS[15]. However, historical research and our contemporary research indicate significant regional differences. In a paper in the Australian Geographer in 1933 Sutton outlined the regional and sub regional differences in iodine deficiency. Taking water as an example, the NNS indicates that water is a major dietary source of iodine contributing 5-

9% of the total daily iodine requirement[16]. A search of historical data would quickly indicate that this was unlikely to be correct. Reading historical research papers led us to undertake a study of iodine levels in Gippsland water (forthcoming). In 2008 we found that the mean water iodine concentration in the Gippsland region is negligible (0.38 µg/L) this means that drinking water would not be a useful dietary source of iodine. Again based on our reading of historical data we undertook a study of the diet of a cohort of pregnant woman in Gippsland. Again the results indicated that this cohort consumed little in the way of iodine rich foods and were iodine deficient. Most significantly historical evidence from Tasmania indicates that supplementation based on the 1995 average Australian dietary iodine levels would result in continued iodine deficiency for pregnant and breast feeding women if based on iodine fortification of bread alone. Again our study confirmed that the current bread iodine fortification program has failed to improve iodine status among Gippsland pregnant women.

We argue that it is clear from historical and contemporary evidence that the current national bread fortification scheme is unlikely to work. Good health care for individuals and the community and good research is based on taking a good history. Research by Hampton et al demonstrates the diagnostic power of taking a good history[3]. Taking a good history is as important in public health research and practice. Archival searches are important as electronic journal/database searches are not always sufficient. The historical and contemporary evidence shows that it is important to recognize regional and sub regional diversity. Public health interventions such as iodine supplementation strategies must be implemented with individual, population and regional differences in mind. The pre and post monitoring of interventions is essential and should be based on a representative sampling frame – this is especially important for regional and sub-regional areas with a history of iodine deficiency.

Government and health authorities should undertake regular monitoring of population iodine status (especially in areas with a history of iodine deficiency). Finally population health study findings and interventions must be adequately documented and stored in an accessible form lest history be forgotten and ineffective programs repeated.

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CHAPTER 4

Paper 2

Is Gippsland environmentally iodine deficient? Water iodine concentrations in the Gippsland region of Victoria, Australia.

Journal: The Australian Journal of Rural Health

Status: Under review (10th of August 2010)

Preface

Usually areas with a history of iodine deficiency disorders also have environmental iodine deficiency. The previous paper confirms the history of iodine deficiency in the Gippsland region. However, we found no studies that examined the environmental iodine status of Gippsland. This paper explores the testing of water samples from water treatment plants and rain water tanks across central, south and west Gippsland. It also reports on the daily dietary iodine contribution of Gippsland tap water and looked for any relationship between iodine concentration and distance from the sea. Findings from this paper indicate that Gippsland is indeed environmentally iodine deficient.

Part B: Declaration for Thesis Chapter

PART B: Suggested Declaration for Thesis Paper

Monash University

Declaration for Thesis Paper 2

Declaration by candidate

In the case of Thesis Paper 2 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, establishment of research database, performing the statistical analysis, writing and editing of the paper	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Nicholas Deacon	Study design, writing and editing of the paper	N/A
Dr. Barbara Panther	Study design, writing and editing of the paper	N/A
Dr. Janice Chesters	Study design, writing and editing of the paper	N/A
Dr. Gayle Savige	Study design, writing and editing of the paper	N/A

Candidate's Signature		Date
	[redacted]	5/08/2010

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Monash University Department of Rural and Indigenous Health, 3 Ollerton Avenue, Moe, VIC-3825

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

	Co-Authors signature	Date
Signature 1	[redacted]	5/08/2010
Signature 2	[redacted]	5/08/2010
Signature 3	[redacted]	5/08/2010
Signature 4	[redacted]	5/08/2010

Manuscript Title: Is Gippsland environmentally iodine deficient? Water iodine concentrations in the Gippsland region of Victoria, Australia.

Names of the Authors: Ashequr Rahman[1], Nicholas Deacon[2], Barbara Panther[2], Janice Chesters[1], Gayle Savige[1]

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Abstract

Iodine is an essential micronutrient for producing thyroid hormones and is important for normal brain development. Australia is an iodine deficient country and Gippsland, a region in the Australian state of Victoria, has a history of iodine deficiency. Water can be a direct source of dietary iodine and an important surrogate marker for iodine deficiency in a population. The cut-off value for water iodine concentrations considered to be indicative of environmental iodine deficiency is < 2µg/L. This paper reports on the iodine concentration of drinking water from sources across Gippsland and examines the contribution of iodine from water to the Gippsland diet. This study also briefly examines the relationship between the concentration of iodine in water and distance from the sea. The mean iodine concentration of water from 18 Gippsland water treatment plants was 0.38 µg/L and would therefore make negligible difference to the dietary intake of iodine. This finding also falls well below the suggested dietary intake of iodine from water estimated by the 22nd Australian Total Diet Study. Our study found no linear relationship between the water iodine concentration and distance from the sea. As Gippsland has environmental iodine deficiency there is a greater probability that people living in this region are at higher risk of dietary iodine deficiency than those living in environmentally iodine sufficient regions. Populations living in areas known to have environmental iodine deficiency should be monitored regularly to ensure that problems of iodine deficiency especially amongst the most vulnerable, are addressed promptly.

Key Words: Environmental iodine deficiency, Gippsland, Australia, drinking water iodine concentration, dietary contribution, distance from sea

What this paper adds

1. **What is already known on this subject**

- Water iodine concentration is an important surrogate marker of environmental iodine deficiency.
- Food Standards Australia and New Zealand makes an average estimation that tap water contributes to 5-9% of daily dietary iodine requirement of Australian population.
- The Gippsland region of Victoria has a long history of iodine deficiency.

2. **What this study adds**

- Water iodine concentrations from the Gippsland region are indicative of environmental iodine deficiency.
- Iodine concentration from Gippsland tap water is very low and contributes virtually nothing to the daily iodine requirement.
- The assumption that the Australian population receives between 5% and 9% of the recommended daily intake of iodine through drinking water is misleading and needs to be amended to allow for regional variations in the concentration of this dietary component.

Introduction

Iodine is an essential micronutrient which plays a crucial role in ensuring the normal development of most organs, especially the brain[1,2,3]. Iodine deficiency is the world's greatest single cause of preventable brain damage and developmental delay and can account for a loss of 10-15 points in IQ even with moderate iodine deficiency[4]. Lack of iodine in the diet, or Iodine Deficiency Disorder (IDD), is a major individual and public health problem in many regions of the world including Australia[5].

In 1948, Gippsland was found to have a high incidence of goitre, a sign of moderate to severe iodine deficiency[6]. Clement's study, along with other studies prompted an iodine supplementation program that was implemented in regions affected by iodine deficiency such as Gippsland[7,8]. Anecdotal evidence suggests the supplementation program ceased after a couple of decades, although official documentation detailing the time and decision to stop the supplementation program cannot be found.

In 2003-2004 the Australian National Iodine Nutrition Study (NINS) found school children in Victoria were not only iodine deficient but also they had the worst iodine status among all the mainland Australian states[9]. This re-emergence of iodine deficiency also confirmed by other studies resulted in the introduction of a mandatory Australia wide iodine supplementation program via bread products[10].

In Australia, the iodine supplementation program was based on assumptions drawn from the best available data. The 22nd Australian Total Diet Study (ATDS) calculated the mean iodine concentration of tap water to be 11.3

µg/L. FSANZ (the national authority that determines the concentration and vehicle for iodine supplementation) estimated that the Australian population would receive 5-9% of its total dietary iodine supply from drinking water[11]. The concentration of iodine in water can be used as a surrogate marker for iodine deficiency in a population since it not only affects the direct intake of iodine from water but also it influences the iodine content of food produced and consumed in the region supporting the population[12]. According to Hetzel and Clugston any region with a water iodine concentration of less than 2.0 µg/L should be considered an environmentally iodine deficient region[12].

A study in Denmark, found that regional differences in the iodine concentration of drinking water correlated with the urinary iodine excretion status of the respective areas' populations[13]. The authors concluded that water iodine concentrations could influence the iodine status of populations and therefore the occurrence of thyroid disorders. This finding confirms the potential consequences of environmental iodine deficiency on the iodine status of a population living in such an area. It also draws attention to the potential problems that might arise when implementing national strategies to overcome iodine deficiency.

It seems likely that the Gippsland would be an environmentally iodine deficient area given its population had a history of iodine deficiency. If Gippsland was an environmentally iodine deficient region, then the modeling used by FSANZ would overestimate the direct intake of iodine from water among those living in Gippsland as well as other populations living in environmentally similar regions. To the best of our knowledge, the iodine concentration of water in Gippsland has not been measured. Our study aims to:

- Examine the iodine concentration of drinking water across the Gippsland region.
- Investigate the potential contribution of iodine from water to the Gippsland diet.
- Investigate the iodine concentration of drinking water obtained from water sources close to the sea to determine if these sources have a higher concentration of iodine than drinking water obtained further inland.

Figure 5: Gippsland water treatment plants and household rain water tanks location

Water treatment plants locations (1 to 18) were: 1: Glen Forbes, 2:Neerim South, 3: Moe, 4: Willow Grove, 5: Thorpdale, 6: Mirboo North, 7: Erica, 8: Congulla, 9: Traralgon, 10: Tyers, 11: Boolarra, 12: Heyfield, 13: Briagolong, 14: Maffra, 15: Sale, 16: Seaspray, 17: Warragul, 18: Morwell.

Rain water tank locations (17-20) were: 17: Warragul, 18: Morwell, 19:Boorool, 20: Jeeralang

Methods

Water sampling

Water samples were collected from 18 water treatment plants across the central, west and southern regions of Gippsland (Figure 5). From each water treatment plant, 50ml samples of both untreated and treated water (suitable for drinking) were collected into polypropylene containers (cleaned with deioinized water). The water samples were collected directly from the separate sources of untreated and treated water and transported to the laboratory on the same day and stored at -20ºC. Samples from four household rain water tanks were collected from outlet taps and transported and stored in the same manner.

Analysis

Water samples were thawed, mixed by inversion and duplicate 1ml aliquots were analysed for iodine concentration using spectrophotometric analysis of Sandell-Kolthoff catalytic reaction products[14]. Each sample batch was accompanied by aqueous potassium iodine standards in the concentration range 0.05 – 1.00µg/L for instrument calibration. The location (longitude and latitude) of the water treatment plants and three of the four rain water tanks was determined using the 'Place name search' tool (GeoScience Australia, Australian Government). The rain water tank located at the Boorool site was determined using a Garmin GPSMAP 60CSx handheld GPS instrument. The distance from the sea of each water treatment plant and rain water tank location was determined using Australian Maritime Spatial Information System (AMSIS) Interactive Mapping Application

(GeoScience Australia, Australian Government). The mapping software used was Arc GIS 9.3 (ESRI, USA). T test (pair wise) and linear regression model were used for test of significance and association and p value <0.05 was considered significant. SAS Enterprise guide 4.1 (SAS Inc., USA) was used as the statistical package.

Results

The concentration of iodine in the water samples obtained from treatment plants in the Gippsland region (Figure 5) ranged from 0.10 to 1.26µg/L for untreated water and 0.11 to 1.07µg/L for treated water (Table 4). The mean iodine concentrations of untreated and treated water, respectively, were 0.41 and 0.38µg/L ($p>0.05$). The mean difference in iodine concentration of untreated and treated water from the same water treatment plant was also not statistically significant. In the case of the rain water tank samples, the water iodine concentration ranged from 0.1 to 0.36µg/L and the mean iodine concentration was 0.24µg/L (Table 5). All water samples had iodine concentrations that were well below the cutoff value (2.0µg/L) indicative of environmental iodine deficiency.

Table 4: Iodine concentration of untreated and treated water in Gippsland

Water treatment plant location	**Distance from the sea (Km)**	**Untreated water iodine concentration (µg/L)**	**Treated water iodine concentration (µg/L)**
Warragul	44.6	0.17	0.33
Neerim South	78.3	0.59	0.23
Moe	74	0.82	0.22
Willow Grove	80.8	0.1	0.4
Thorpdale	60.8	0.42	0.51
Mirboo North	50.2	0.26	0.21
Erica/Rawson	90.2	0.1	0.27
Morwell	64.9	0.13	0.18
Traralgon	61.9	0.1	0.11
Tyers	69.9	0.43	0.41
Boolarra	58	0.87	0.59
Heyfield	63.2	0.63	0.47
Coongulla	69.8	0.29	0.15
Briagolong	56	0.22	0.33
Maffra	52.1	0.21	0.35
Sale	35.2	1.27	1.07
Seaspray	6.9	0.1	0.25
Glen Forbes	18.4	0.84	0.78
Mean (lower 95% CL for mean-upper 95% CL for mean) ± SD		0.42 (0.25-0.59)±0.34	0.38 (0.26-0.50)±0.24

All the water treatment plants source untreated water from surface water, except Briagolong and Sale source their water from groundwater. Thorpdale's water comes from both surface and ground waters.

Table 5: Iodine concentration of household rain water tank water

Location	Distance from the sea (Km)	Water Iodine concentration (µg/L)
Boorool	42.3	0.25
Jeeralang	46.0	0.10
Morwell	64.9	0.36
Warragul	44.6	0.24
Mean (lower 95% CL for mean-upper 95% CL for mean) ± SD		0.24 (0.07-0.41)±0.11

The World Health Organization (WHO), estimates the average daily drinking water requirements for younger children and adults is one and two litres, respectively[15]. If these amounts are used to estimate the intake of iodine from drinking water derived from Gippsland, infants would consume only 0.38 µg of iodine (<1% of the recommended daily intake of iodine for this population group) and adults would consume only 0.76 µg of iodine (<1% of the recommended daily intake of iodine). These results show that the amount of dietary iodine obtained from drinking water in Gippsland falls well below the estimates (of 5%-9%) suggested by the 22nd Australian Total Diet Study.

Table 6: Calculation of daily dietary intake of iodine from tap water for Australian population

(data extracted for Column 1, 2 and 3 from the 22nd Australian Total Diet Study, 2008[11])

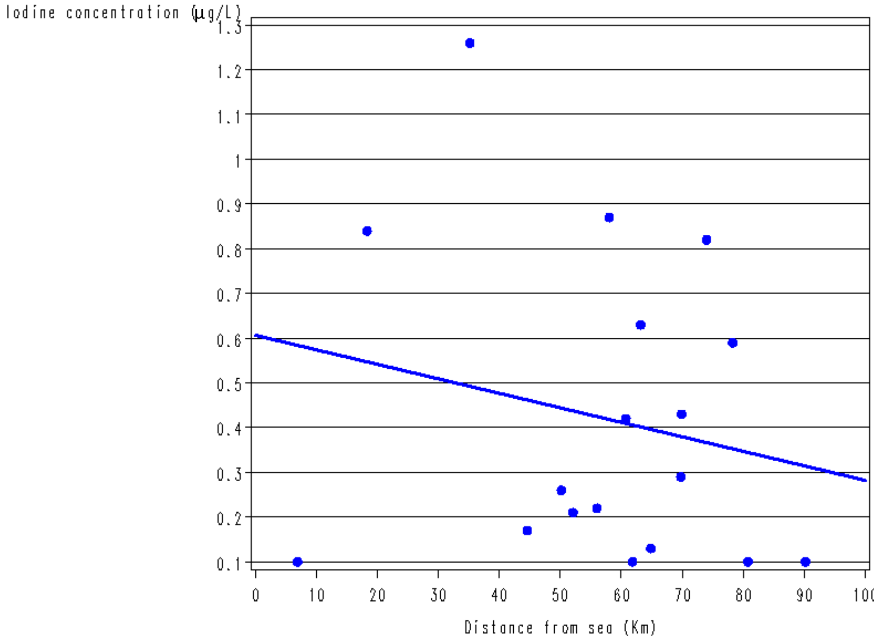
Age group	**Mean lower bound intake (µg/day)**		**Percent contribution of water to total intake of Iodine**		**Calculated amount of Iodine received from Australian tap water (µg/day)**	
	Male	Female	Male	Female	Male	Female
Infant	57.8 (middle bound intake)		5		2.89	
2-3 yrs	96.2	82.9	4	4	3.85	3.32
4-8 yrs	99.4	78.1	5	6	4.97	4.69
9-13 yrs	110.3	84.5	6	6	6.62	5.07
14-18 yrs	127.8	84.8	6	8	7.67	6.78
19-29 yrs	120.3	85.1	7	9	8.42	7.66
30-49 yrs	102.3	81.4	7	9	7.16	7.33
50-69 yrs	94.6	78.1	6	8	5.68	6.25
70+yrs	86.0	74.8	6	8	5.16	5.98

The geospatial location of Gippsland allowed us to determine if there was a linear relationship in iodine concentrations in water with increasing distance from the sea using a linear regression model. The results were not statistically significant for untreated water drawn from the treatment plants ($p = 0.43$, R-square = 0.04) (Table 4 and Figure 6A) and for water drawn from rainwater tanks (p = 0.31, R-square = 0.46) (Table 5 and Figure 6B).

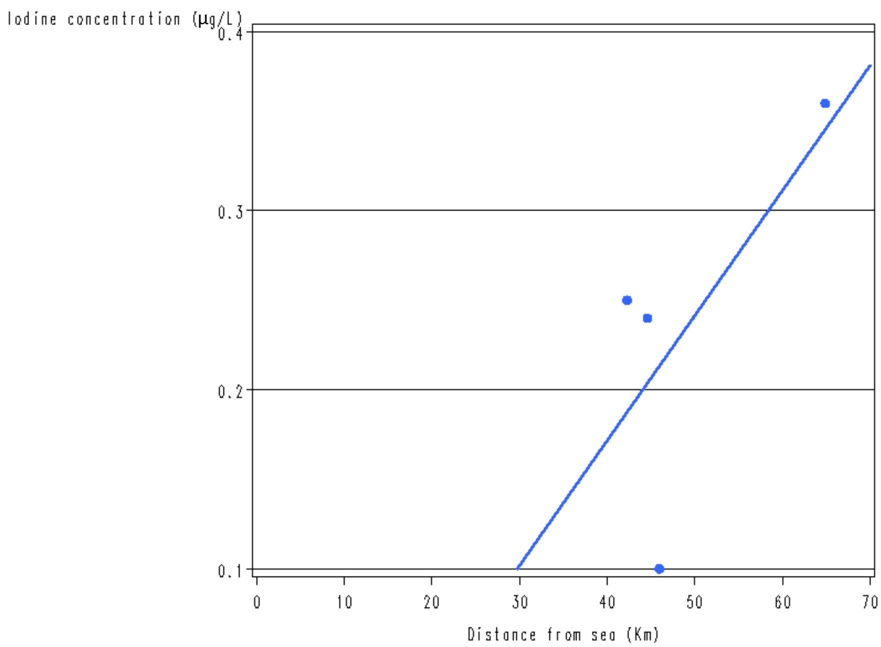
Our results did not demonstrate a linear relationship between water iodine concentration in Gippsland and the distance from the sea.

Figure 6: Linear regression plot for water iodine concentration and sea distance from (A) location of the water treatment plants and (B) location of household rain water tank

A.



B.



Discussion

Differences in water iodine concentration are due to different geological structure in the aquifer source rock and type of soil. A Danish study found a high concentration of iodine (140 µg/L) in the water of one town (Skagen) where the aquifer source rock contained marine deposits but low concentrations (2 µg/L) in another town of close proximity (Randers) where the rock aquifer source was different[16]. In Derbyshire, UK, the surface water from an active fluorspar mining area showed higher iodine concentrations (7.3 µg/L) compared to water sourced from carboniferous limestone areas (2 µg/L) thus indicating surface water was closely related to soil iodine[17].

Most of the tap water that was tested from Gippsland was sourced from surface water (rivers and lakes) that runs off many different soil types of unknown soil iodine concentration. However, it has been suggested the Australian soils are likely to be iodine deficient as the soils have not been sufficiently saturated with postglacial air -borne iodine (WHO, 1960). In Victoria, uplift associated with the Tabberabberan Orogeny (a mountain building and deformation process, 395-385 million years ago) caused the sea to move away to the east and that resulted in cessation of all marine sedimentation in Victoria[18].

A study in Zhejiang, China, found the concentration of environmental iodine in soil and water decreased with increasing distance from the sea[19]. However, in our study we did not find such a relationship with water iodine concentrations and in a UK study, Whitehead did not find any correlation between iodine concentration in soil and distance from the sea[20].

At a mean iodine concentration of 0.38ug/L for treated water Gippsland is an environmentally iodine deficient region. Low iodine concentration in drinking water has been identified as an important factor in the incidence of iodine deficiency disorders[12, 21, 22, 23]. The water iodine concentration in the Gippsland region (0.38µg/L) shows a similar water iodine concentration to that in the Xinjiang province of China, a region known for environmental iodine deficiency and endemic goitre. In the province of Wushi, the water iodine concentration was 0.01 – 3.7µg/L and the total soil iodine concentration in that region was 0.03µg/g[21]. Presumably crops grown in such iodine deficient regions will be poor sources of iodine. Similarly, low iodine levels affect animal production and animal health. A study in Sri Lanka found an inverse association between water iodine concentrations and the prevalence of goitre and concluded the difference in water iodine concentrations was the most likely reason for the difference in goitre rates[22].

The 22nd Australian Total Diet Study identified tap water as a source of iodine for the Australian population providing between 2.9 and 8.4 µg iodine per day, depending on age and sex[11]. But as we have shown water iodine concentrations in Gippsland are much lower than those estimated by the ATDS and are consistent with environmental iodine deficiency. Water is a negligible source of dietary iodine for the Gippsland population and as such the estimates of iodine intake applied nationally may not be appropriate for this population (or other populations living in other regions with a history of iodine deficiency).

As Gippsland has environmental iodine deficiency there is a greater probability that people living in this region will be at higher risk of dietary iodine deficiency than populations living in other regions (not deemed environmentally iodine deficient). This anticipated increase in risk requires further investigation to ensure iodine deficiency is adequately addressed by the mandatory bread fortification program in these areas. If not, a more targeted approach to dietary iodine supplementation especially among the groups most at risk of iodine deficiency may be required such as pregnant and lactating women and their infants.

Conclusion

1. Water iodine concentrations (mean 0.38µg/L) in Gippsland indicate drinking water is a very poor dietary source of iodine.
2. As water iodine concentrations are an important surrogate marker of environmental iodine deficiency regional variations should be taken into account when calculating the contribution of iodine from different dietary sources.
3. The assumption that the Australian population receives between 5% and 9% of the recommended daily intake of iodine through drinking water is misleading and needs to be amended to allow for regional variations in the concentration of this dietary component.

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None of the authors had a personal or financial conflict of interest.

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CHAPTER 5

Paper 3

Increased iodine deficiency in Victoria, Australia: Analysis of neonatal TSH data 2001 to 2006

Journal: Medical Journal of Australia

Status: In Press (2nd of August 2010)

Preface

People living in a region known to be environmentally iodine deficient are at risk of developing iodine deficiency. It is important to monitor population iodine status regularly, especially in iodine deficient regions. The previous paper indicated that Gippsland is an environmentally iodine deficient region. This paper researched the population iodine status of the Gippsland region as well Victoria, as a whole by retrospective analysis of neonatal Thyroid Stimulating Hormone (TSH). Neonatal TSH level is a cost effective way of monitoring population iodine status. This testing should be done regularly and analysed at the local, regional, state and national level.

Part B: Declaration for Thesis Chapter

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter 3

Declaration by candidate

In the case of Chapter 3 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, establishment of research database, performing the statistical analysis, writing and editing of the paper	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Gayle Savige	Study design, writing and editing of the paper	N/A
Nicholas Deacon	Study design, writing and editing of the paper	N/A
Ivan Francis	Study design, advise on Victorian neonatal database and comment on drafts of the paper	N/A
Janice Chesters	Study design, writing and editing of the paper	N/A

Candidate's Signature	[redacted]	Date 7/05/2010

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Monash University Department of Rural and Indigenous Health, 3 Ollerton Avenue, Moe, VIC-3825

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]		**Date**
Signature 2			7/05/2010
Signature 3			7/05/2010
Signature 4			7/05/2010

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Abstract

Background: Australia is an iodine deficient country. To address this problem a national, mandatory bread iodine fortification program was introduced in 2009. Regular monitoring of population iodine status is essential to measure the effectiveness of this bread supplementation program. Currently there is no monitoring program to measure iodine status and nor is one planned.

Objective: To carry out a retrospective analysis of the Victorian Neonatal Thyroid Stimulating Hormone (TSH) database to measure population iodine status and test the effectiveness of this method as an economic and accurate monitoring tool.

Design: 368,552 Victorian neonatal TSH blood sample results were analysed according to health regions for the years 2001 to 2006. The mean percentage of neonatal TSH above 5 mIU/L was calculated for the sample.

Results: The population from all health regions in Victoria, Australia showed increasing iodine deficiency. The mean percentage of neonatal TSH above 5 mIU/L ranged from 4.07 in 2001 to 9.65 in 2006 and the difference was statistically significant ($p<0.001$). Populations from metropolitan regions had higher iodine deficiency concentrations than non-metropolitan regions and this difference was also statistically significant ($p<0.05$). These results were consistent with Urinary Iodine Excretion (UIE) research in Victoria.

Conclusions: The TSH results are of concern and require ongoing monitoring. Measuring neonatal TSH concentrations offers an effective and

economic method of monitoring population iodine status in this vulnerable group and is an excellent proxy indicator of population iodine status as a whole. It should become part of the regular neonatal screening program in Australia.

Key words: Iodine deficiency, Victoria Australia, neonatal TSH, monitoring

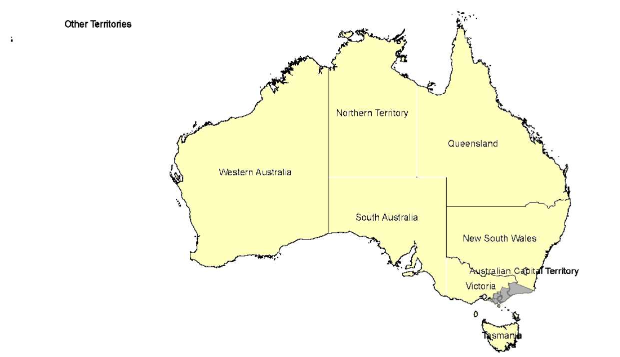
Introduction

Iodine is an essential micronutrient which plays a crucial role in ensuring the normal development of most organs, especially the brain[1-3]. The World Health Organization (WHO) reports that even moderate iodine deficiency can cause a loss of 10-15 points in IQ and it is the world's greatest single cause of preventable brain damage and developmental delay[4]. Lack of iodine in the diet or Iodine Deficiency Disorder (IDD) is a major individual and public health problem in many regions of the world. The WHO global database on Iodine deficiency lists Australia as one of the world's 54 iodine deficient nations[5].

In order to address Australia's iodine deficiency, Food Standards Australia and New Zealand (FSANZ) has recently introduced a mandatory, Australia wide, iodine supplementation program via bread products. Although this supplementation program is based on strong evidence of iodine deficiency from a small number of regional Urinary Iodine Excretion (UIE) studies there has been no Australia wide pre supplementation baseline data study (the only National Iodine Nutrition Study, NINS, was conducted in 2003-2004)[6]. In addition, although the Australian Institute of Health and Welfare

(AIHW) has recommended post-supplementation monitoring using the UIE method, no Australia wide monitoring program has yet been announced[7].

Figure 7: Map of Australia. The Gippsland region of Victoria marked in gray



As the debate in Australia regarding supplementation was progressing we were coincidently carrying out a four part iodine research project in Gippsland, a region in the Australian state of Victoria. A key part of this study involved a retrospective Neonatal TSH data analysis of the cohort of babies born in Victoria from 2001 to 2006. These data provide baseline information on the iodine status of the neonatal population of Victoria that can be compared with the post iodine fortification period in Victoria.

Routine neonatal blood screening for metabolic and genetic disorders in Australia, and many other countries, includes the determination of neonatal TSH concentrations. In five separate large studies in Switzerland, Poland, Bulgaria, Belgium and Thailand it was found that TSH monitoring could offer an effective method for monitoring population iodine status[8-12]. In a recent review article Zimmermann urged that a confirmation study of the sensitivity of this method of monitoring iodine fortification be carried out in an iodine sufficient country with a newborn screening program[13]. Our study provides baseline information on the iodine status of the neonatal population of Victoria which will allow comparison with the post iodine fortification period in Victoria. Indeed, Victorian neonatal TSH concentrations are consistent with previous studies indicating population iodine deficiency[6, 14].

Methodology

In Australia, heel prick blood samples are collected routinely from newborns at 2 or 3 days of age and the TSH concentration is determined by the immunoassay technique[15]. Since 1977 Victorian newborn blood TSH concentrations have been determined individually at the Victorian Clinical Genetics Laboratory (VCGS) and recorded on a database arranged according to the birth-hospital postcode (a unique 4 digit number used for mail delivery). The latest audit of compliance with the heel prick test was conducted in 2002 and showed that more than 99.4% of Victorian neonates received a screening test[16]. The TSH kit used was the Elegance neonatal TSH kit and the samples were analysed using a Labsystems Multiskan RC plate reader.

The Victorian neonatal TSH values, birth hospital postcode, sex, date of birth, time of taking the blood sample and twin information from the last 30 years was extracted from the Victorian neonatal database. However, complete full year neonatal TSH data analysis was done for the years 2001 to 2006. The total number of individual neonatal blood TSH values analysed during the period was 379,735. We excluded 11183 individual neonatal TSH values due to repeat sample tests and blood samples taken after 96 hours of birth. This left 368,552 cases, representing approximately 61,425 tests per year over the period. According to the Victorian Birth Register the total number of births in Victoria from 2001 to 2006 was 388,642[17]. Compared with that given number, our individual neonatal TSH values represent 94.83% of the total neonatal population.

De-identified Neonatal TSH values were analysed using the World Health Organization (WHO)/United Nations Children's Fund (UNICEF)/ International Centre for Control of Iodine Deficiency Disorder (ICCIDD) criteria and the percentage of neonatal TSH values greater than 5mIU/L for each year were calculated. The data were arranged by birth hospital, postcode and then re-grouped into the nine Department of Human Services geographical regions of Victoria using SAS Enterprise Guide 4.1 software (SAS Institute Inc., USA) and ArcMap 9.3 (ESRI Inc., USA) was used as mapping software. The Chi square test was used to determine the statistical difference in the frequency distribution of TSH values >5mIU/L and a *p*-value of <0.05 was considered statistically significant. Ethics approval was obtained from the Royal Children's Hospital, Melbourne and the Monash University Human Research Ethics Committee.

Results

The mean percentage of Victorian neonatal TSH concentrations above 5mIU/L ranged from 4.07% in 2001 to 9.65% in 2006 (Figure 8) indicating an iodine deficient status according to the WHO, UNICEF and ICCIDD criteria, for that period. Furthermore, this 2.37 fold increase over five years was statistically significant ($p<0.001$) for 2001 to 2006 and for each of the year on year increase.

Neonatal TSH values were grouped into the nine Department of Human Services health regions in Victoria and the percentage above the 5mIU/L concentration re-plotted (Figure 9). Our focus was on the Gippsland region and the percentage of Gippsland neonatal TSH values >5mIU/L increased from 3.54 in 2001 to 8.37 in 2006. This 2.36 fold increase was statistically significant ($p<0.001$). However, our analysis indicated that the IDD status of all nine Department of Human Services health regions in Victoria had worsened over the period 2001 to 2006 (Figure 8 & Figure 9). Among the regions, the metropolitan areas all had a higher percentage of newborns with blood TSH concentrations >5 mIU/L than the non-metropolitan areas and this was statistically significant ($p<0.05$). The Northern metropolitan region had the highest frequency of neonatal TSH values >5mIU/L at 11.01% in 2006. Within each region the differences between the years 2001-2006 were statistically significant ($p<0.001$). Additionally, the year on year increase for each region was statistically significant ($p<0.05$) and the difference between regions was statistically significant ($p<0.05$).

Figure 8: Mean percentages of Neonatal TSH >5 mIU/L in Victoria from 2001 to 2006.

Vertical bars represent standard error of mean.

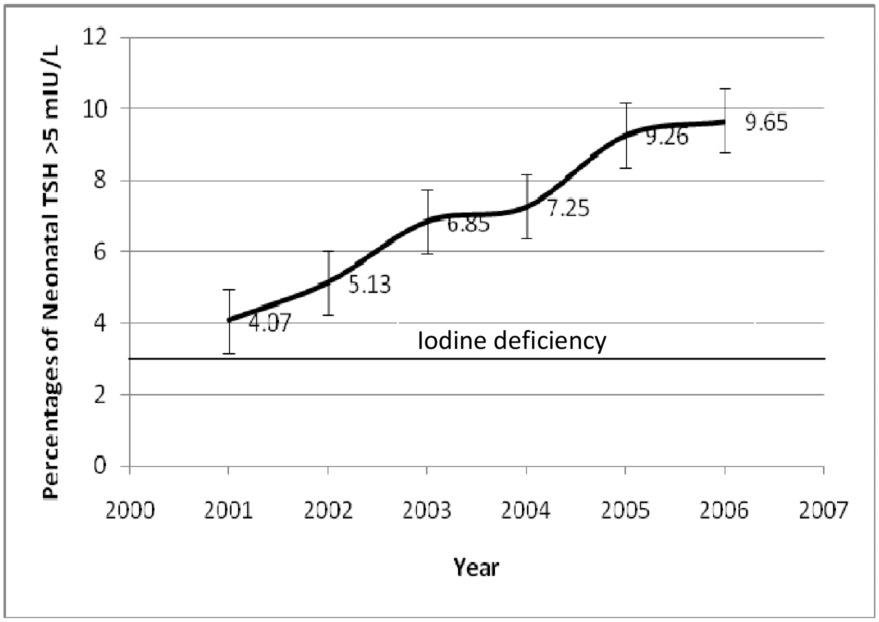
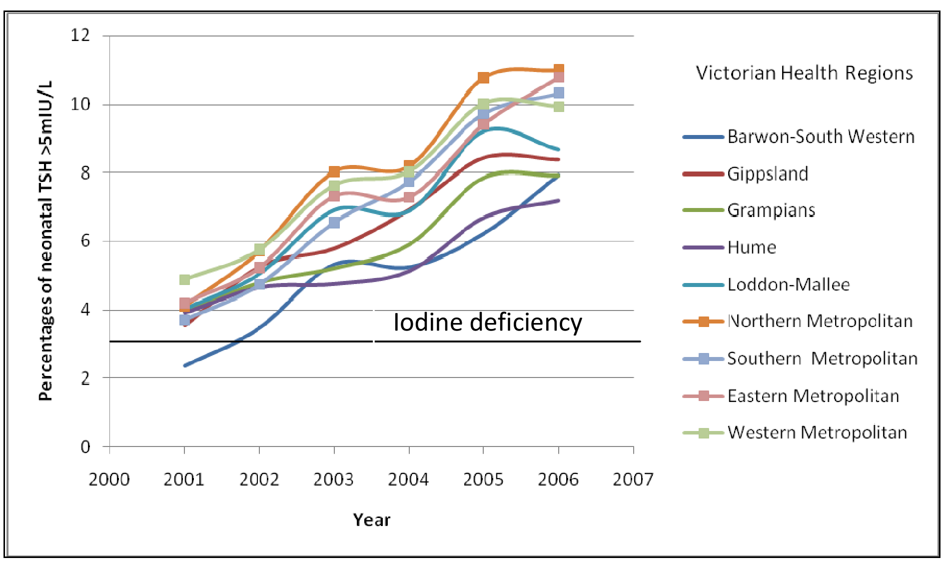


Figure 9: Mean percentages of Neonatal TSH >5 mIU/L in the nine Victorian health regions from 2001 to 2006.

Metropolitan regions are highlighted by square symbols.



Discussion

This analysis of 368,552neonatal TSH concentrations representing more than 94.83% of Victorian children born during 2001 to 2006 indicates that this population is iodine deficient according to the WHO, UNICEF and ICCIDD criteria. This result is consistent with three smaller Australian studies utilising newborn TSH data from Sydney in the Australian state of New South Wales. One Sydney study conducted in 1998-1999, found that 8.1% of newborns (n=1316) and 5.5% of newborns (n=1457) had TSH values >5 mIU/L[18]. The second Sydney study, carried out in 2002-2003 found that 7.1% of newborns (n=651) born by caesarian section and 4.3% of newborns (n=1380) born by vaginal delivery had TSH levels above >5 mIU/L[19]. The third Sydney study, carried out in 2005 (n=816), found only 2.2% of newborns with TSH values above 5 mIU/L. However, the results of an UIE study of pregnant women from the third study, carried out at the same time, indicated iodine deficiency[20]. All studies, however, were based on small sample numbers collected over a short period of time (less than a year). This study has findings that are also consistent with the results of two UIE studies[6, 14]. The 2003-2004 National Iodine Nutrition Study (NINS), which included 348 Victorian school children, and a study of school children in Melbourne, Victoria (n=577) conducted in 2003 and 2001, respectively. Both studies found that Victorian school children had urinary iodine excretion concentrations indicative of mild iodine deficiency, according to WHO/ UNICEF/ ICCIDD criteria.

Some factors that might affect the newborn TSH concentrations, these include age at the collection of blood samples, thyroid hormone supplementation during pregnancy and exposure to iodine-containing disinfectants during delivery. Effects due to iodine based disinfectants during delivery or thyroid hormone therapy during pregnancy could not be ruled out as this data were not recorded in the neonatal database. However, the data analysis followed the standard guidelines for age at collection blood samples and only included the blood samples those were taken between 48-96 hours of birth[21-24].

WHO, UNICEF, ICCIDD and national food standards authorities, such as FSANZ, have emphasized the need for regular monitoring of population iodine status. The UIE assay, although recognised as the 'gold standard' test, is expensive in time, cost, personnel and effort. We suggest that the regular analysis of routine neonatal population screening TSH test results is an easier and less expensive method for monitoring iodine deficiency in the most vulnerable population group (pregnant women). These data are collected as part of an on-going national population screening program for congenital diseases and therefore it provides an opportunity for regular and continual monitoring of this population's iodine status. This approach has been used very effectively to monitor the beneficial effects of the Swiss iodised salt program[9]. An additional advantage with this method is its flexibility as the monitoring may be carried out annually, monthly or on an ongoing basis as part of a national, state by state or regional monitoring program. This offers the additional advantage of being able to detect potential iodine deficiency 'hot spots' using the birth hospital postcode as a locator.

We suggest that the neonatal TSH concentrations in all states of Australia be analysed as soon as possible and this analysis should become a regular part of neonatal screening program in Australia.

Acknowledgement

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CHAPTER 6

Paper 4

Urinary iodine deficiency in Gippsland pregnant women: The failure of bread fortification

Journal: Medical Journal of Australia

Status: Under review (8th of August 2010)

Preface

The iodine requirement during pregnancy is almost double that of an adult. For that reason, pregnant women are at risk of developing iodine deficiency if they do not eat an iodine rich diet or take appropriate supplements. The previous paper showed iodine deficiency among the newborn population in the Victoria, which is indicative of iodine deficiency in pregnant women during their last trimester. This paper looks at the iodine status of pregnant women across the Gippsland region. It uses urinary iodine concentration (UIC) measurement. As the urine samples were collected before and after the national bread fortification program which was implemented in October 2009, it provided a rare opportunity for an early assessment of this program. Information on the pregnant women's diet, supplement intake and knowledge of the importance of iodine was also collected. The evidence shows that the current national bread fortification plan will not provide enough iodine for pregnant women.

Part B: Declaration for Thesis Chapter

PART B: Suggested Declaration for Thesis Paper

Monash University

Declaration for Thesis Paper 4

Declaration by candidate

In the case of Thesis Paper 4 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, establishment of research database, performing the statistical analysis, writing and editing of the paper	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr. Gayle Savige	Study design, writing and editing of the paper	N/A
Dr Nicholas Deacon	Study design, writing and editing of the paper	N/A
Dr. Janice Chesters	Study design, writing and editing of the paper	N/A
Dr. Barbara Panther	Study design, writing and editing of the paper	N/A

Candidate's Signature		Date
	[redacted]	6/08/2010

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Monash University Department of Rural and Indigenous Health, 3 Ollerton Avenue, Moe, VIC-3825

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

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Signature 4	[redacted]	6/08/2010

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Abstract

Objective: To assess the iodine status and iodine rich food intake of a cohort of Gippsland pregnant women before and after the start of the national iodine fortification program.

Design: A cross sectional study.

Setting: Hospital antenatal care services and private obstetrician clinics in the Gippsland region of Victoria, Australia. January 2009 to February 2010.

Participants: 86 pregnant women (≥28 weeks gestation).

Main outcome measures: World Health Organization/ International Council for the Control of Iodine Deficiency Disorders urine iodine concentration (UIC) criteria for assessing iodine status among pregnant women (median UIC ≥150 µg/L) before and after the national iodine fortification program. A brief pregnancy dietary questionnaire was also administered**.**

Results: The median UIC for these pregnant women was 96 µg/L (inter quartile range 45-153 µg/L) indicating mild iodine deficiency. Only 27.9% women had an adequate UIC above 150 µg/L. The median UIC in the pre-fortification period was 96 µg/L (IQR 45-153µg/L) and in the fortified period it was 95.5 µg/L (IQR 60-156 µg/L). There was no statistically significant difference in the UIC between the pre- fortification and fortified period. The cohorts dietary intake of iodine rich food/ supplements was inadequate to supply required amount of iodine during pregnancy.

Conclusions: The UIC results in this cohort are of concern. The fortified UIC results indicate that the national iodine fortification program will not deliver an adequate amount of iodine during pregnancy. Both knowledge about the importance of iodine and an increased iodine intake during pregnancy is in urgent need of improvement.

Key words: Iodine deficiency, Victoria Australia, pregnant women, urinary iodine concentration (UIC), monitoring

Introduction

Iodine is an essential micronutrient that plays a crucial role in ensuring the normal development of most organs, especially the brain[1-3]. The World Health Organization (WHO) reports that even moderate iodine deficiency can cause a loss of 10-15 IQ points and is the world's greatest single cause of preventable brain damage and developmental delay[4]. For this reason, maintaining an adequate iodine status is crucial for everyone but it is especially important for pregnant and breast feeding women. During pregnancy iodine requirements are almost doubled and therefore iodine deficiency is much more likely among this group[5]. Lack of iodine in the diet or Iodine Deficiency Disorder (IDD) is a major individual and public health problem in many countries including Australia[6]. The Gippsland region of Victoria has a long history of iodine deficiency. In 1960, Gippsland was described in a WHO monograph series on endemic goitre as the 'home of goitre'. Despite this history the Gippsland population has not been screened for iodine deficiency since 1948.

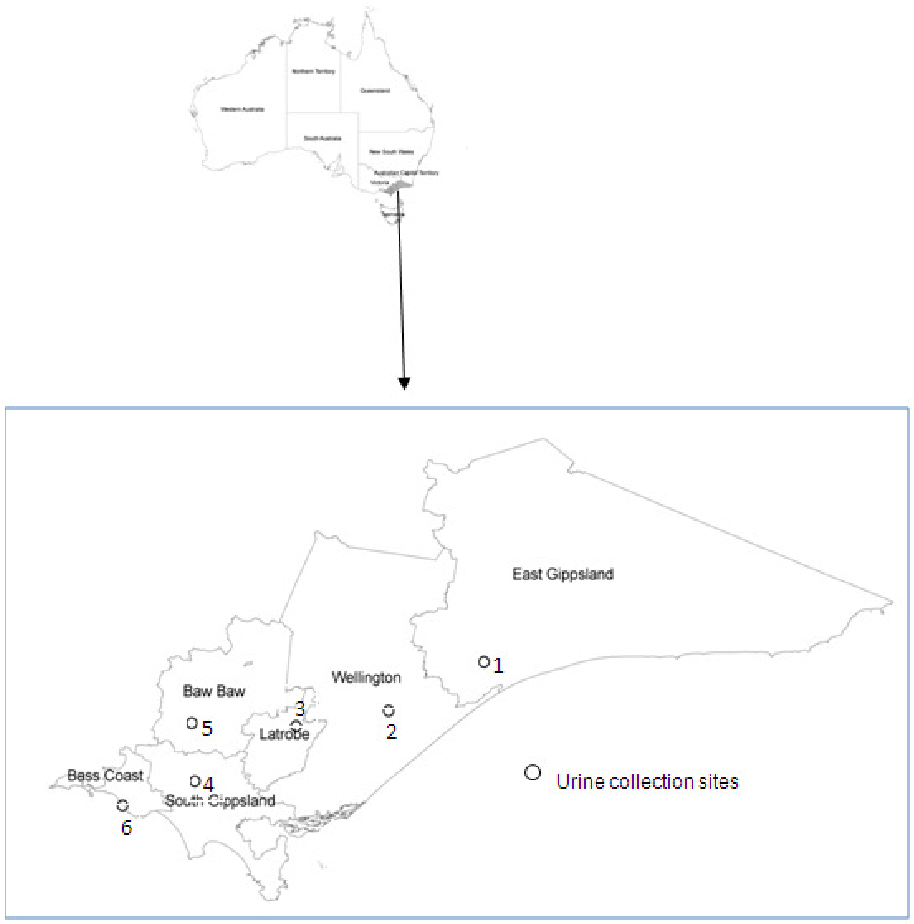
Urinary iodine concentration (UIC) is considered to be the most practical biochemical marker for monitoring population iodine status[4]. The weighted median urinary iodine concentration from the Australian National Iodine

Nutrition Study on school children conducted in 2003-2004 was found to be 96µg/L thus indicating the Australian population was mildly iodine deficient[7]. In order to address this deficiency, Food Standards Australia and New Zealand (FSANZ) introduced mandatory bread iodine fortification via bread products in 2009.

Prior to the bread fortification program we had decided to undertake a cross-sectional urinary iodine study in a cohort of pregnant women across Gippsland. In addition we also wanted to collect data on the women's diet during pregnancy. Only one Australian study of pregnant women has collected data on dietary sources of iodine and the use of supplements[8]. Our study started on the 13th of January 2009 and finished on the 17th of February 2010 thereby overlapping the initiation of the national bread iodine fortification program on the 9th of October 2009. This enabled us to complete an early assessment of the efficacy of this program.

This paper will report on the urinary iodine concentrations of a cohort of pregnant women living in Gippsland, their intake of iodine from foods known to be a good source of iodine, as well as their self reported use of supplements and their estimated intake of bread (both pre and post iodine fortification).

Figure 10: Sample collection sites in the six Gippsland shires:



Methods

This cross-sectional study examined the urinary iodine excretion concentrations of a cohort of pregnant women from all six Gippsland local government areas (Figure 10). The participants were asked to provide a morning urine sample and fill out a self-reported dietary questionnaire. However, 30% of urine samples were collected on the spot to ensure that all pregnant women participating in the study had provided a urine sample. The study sample size calculation (n=86) followed the methods described by Anderson et al[9]. The formula used for the sample size calculation was:

$n = (Z \times CV\%D)^2$ where the Confidence Interval (Z) for 90% was 1.64; CV% (variance square root divided by mean, as a percentage) at the population level was 56.4; D (the precision range) was ±10%.

The eligibility criteria for inclusion in the study were: residents living in Gippsland who were over the age of 18 and who were pregnant at or over the 28th week and were not taking any thyroxin hormone medication. Urine samples were collected at antenatal clinics from four hospitals (Latrobe Regional, Wonthaggi, Leongatha and Warragul) and from three private clinics (Leongatha Medical Centre, Macleod Street Medical Centre in Bairnsdale and the Gippsland Obstetrics and Gynaecology Centre in Sale).

The pregnant women at the antenatal clinics were approached to participate in the study by AR and those who gave their informed consent were provided with a sample collection kit and asked to bring the samples back at their next visit to the hospital or clinic. They were also asked to complete a short questionnaire on their diet. On the day of collection, the urine samples were transported in an ice box to the School of Applied Science and Engineering at Monash University Gippsland and stored at -20ºC. Samples were later sent as a batch to the Institute of Clinical Pathology and Medical Research at Westmead Hospital, NSW for analyses. The cold chain for urine samples was maintained throughout transportation.

The urinary iodine concentration was determined by the modified acid digestion method based on the Sandell-Kolthoff Catalytic reaction[4]. The laboratory at Westmead is the International Centre for Control of Iodine Deficiency Disorders (ICCIDD) reference laboratory for the Asia-Pacific region for measuring urinary Iodine concentration and is accredited by the National Association of Testing Authorities in compliance with International Organization for Standard/ International Electrotechnical Commission standard 17025.

All the UIC cut-off values used in this paper follow WHO/UNICEF/ICCIDD guidelines[10]. T test, Chi-square test and Wilcoxon Test (for non-parametric data) were used for tests of significance and $p<0.05$ was considered as significant. The study was approved by the Human Research Ethics Committees of Monash University, Latrobe Regional Hospital and West Gippsland HealthCare Group and permission was obtained from all other participating hospitals and clinics.

SAS Enterprise Guide 4.1 (SAS Inc. USA) was used for statistical data analysis and ArsGIS 9 (ESRI, USA) was used as the mapping software.

Results

Participant's characteristics

The total number of participants was 86 with a mean age of 29.4 years (SD 4.6 years and age range 19-40 years). The majority of the participants who recorded their ethnicity were Caucasians (93.5%, n=58). The remaining participants (n=4) were from Chinese, Filipino, Indian and Maori ethnic origin. All the participants were in their third trimester of pregnancy (≥28 weeks). Among the participants, 24 (27.9%) provided urine samples before the start of the national bread fortification program.

Urinary iodine concentration

The median urinary iodine concentration (UIC) of the pregnant women was 96.0 µg/L and the inter quartile range (IQR) was 56-156 µg/L (Table 7). From the total cohort (n= 86), 28% had UIC≥150 µg/L which is indicative of adequate iodine status (during pregnancy). The majority (72%) of women had a UIC consistent with iodine deficiency. The 24 urine samples collected before the bread fortification program had a median UIC of 96.0 µg/L while the 62 collected after commencement of bread fortification had a median UIC of 95.5 µg/L. There was no statistical difference between these UIC ($p=0.51$). The median UIC of the participants taking vitamin and mineral supplements containing iodine (n=44) was 121.5 µg/L (IQR 81.5-179.5) while that of the group taking supplements not containing iodine (n=42) was 64.5 µg/L (IQR 50.0-115.0). The difference was statistically significant ($p < 0.001$).

Table 7: Median Urinary Iodine Concentrations of the total, pre-fortified and fortified bread periods

Urine Sample Collection Period	Median UIE (IQR)* µg/L	Proportion of samples with median UIC<50µg/L (%)	Proportion of samples with median UIC ≥150 µg/L (%)
Pre bread fortification period (n=24)	96 (45-153)	29.2 (7)	25.0 (6)
Fortified bread period (n=62)	95.5 (60-156)	12.9 (8)	29.0 (18)
Total (86)	96 (56-156)	17.4(15)	27.9 (24)

*Inter Quartile Range

Dietary sources of iodine

We asked the pregnant women about their consumption of foods that are known to be sources of iodine during their current pregnancy. Foods that were good sources of iodine and were consumed daily or on two-to-three days per week were included in the iodine food frequency calculation. Milk, milk products and (fortified) bread were the most common food sources of iodine among the participants with >94% consuming these foods. There was no significant difference in the consumption of these foods in the pre fortification and iodine fortification periods. Use of iodised salt was found to be lower in the participants who were surveyed after the commencement of the bread fortification program (32.2%) compared with those surveyed prior to fortification (50%). Eggs, as a moderate but important source of iodine, were eaten by about 50% of the women. Among the foods known to be high in iodine (seafood, seaweed and sushi) only ~10% of women reported eating seafood in both the pre and fortified periods; seaweed and sushi made the least contribution as a high iodine source in the pregnant women's diet. Drinking water (from the tap) has been documented as an important source of iodine by FSANZ[10]. More than 70% of the respondents reported drinking tap water, while 14% consumed tank water and 12% drank bottled water.

According to the current bread fortification program, a slice of bread (average weight 30 gm) will provide 10-25µg of iodine[11]. The results of our survey found the median intake of bread was two slices per day (Table 8). The maximum number of slices consumed was 8 slices per day (representing 1.2% of those surveyed). There was no significant difference in bread consumption between pre and fortified periods. The women reported that they maintained the same food habits during previous pregnancies.

Table 8: Daily average bread consumption

Bread consumption (Slices/ day)	All respondents (%)	Pre bread fortification period respondents (%)	Fortified bread period respondents (%)
1	8.6	8.7	8.6
2	48.2	47.8	48.3
3	18.5	17.4	19.0
4	22.2	26.1	20.7
>4	2.5	0.0	3.4
Median	2 slices/day	2 slices/day	2 slices/day

Iodine containing supplements and dietary iodine knowledge

More than 51% of the pregnant women were taking self-administered mineral and vitamin supplements containing 25 to 300 µg of iodine. The consumption frequency was higher in women sampled during the pre-fortification period (54.17%, n=13) than the fortified bread phase (50.0%, n=31). About 42% (n=28) of the respondents mentioned starting supplements before pregnancy. Among the supplements taken only 51.2% (n=23) of women mentioned taking supplements containing 250µg of iodine. The advice to take iodine containing supplements mostly came from doctors (48%, n=31) or was self-initiated (30%, n=20). All the respondents reported hearing about the importance of folic acid during pregnancy, but only 33% (n=28) reported hearing about the importance of iodine.

Discussion

The median UIC of these Gippsland pregnant women (96 µg/L) was indicative of mild iodine deficiency which is in line with the findings of other Australian studies[7,8,12,13]. This study also suggests pregnant women living in Gippsland probably have a history of consuming insufficient iodine via their food. They also lack awareness of the importance of iodine in the diet, especially during pregnancy. Fortuitously, our study spanned the time before and after the commencement of a national bread iodine fortification program in mainland Australia therefore allowing an early assessment of the efficacy of the bread fortification program. There was no statistically significant difference between the UIC results of the pre-fortification and post fortification period indicating that bread fortification is unlikely to meet the increased iodine needs of pregnant women living in Gippsland.

The proportion of the sample of pregnant women living in Gippsland who were iodine deficient (UIC<150 µg/L) was 72%, which reflects the same proportion of iodine deficient school children (UIC<100 µg/L) found in Victoria in the National Iodine Nutrition Study (NINS)[7] The total percentage of the study sample with UIC <50 µg/L was 17.4. A previous study investigating the iodine status of pregnant women in Victoria showed that median UIC for Caucasian women from Melbourne was 52µg/L[12]. According to the WHO criteria, in an iodine replete population, no more than 20% of the population should fall below 50 µg/L[4]. However, due to altered physiology during pregnancy, Stillwell et al. proposed that the proportion of pregnant women with results below 50 µg/L should be less than 10%[14].

Our study results are consistent with other urinary iodine studies on pregnant women across Australia[8,13,15]. Burgess et al (2007) conducted a pre and post iodine bread fortification study in Tasmania on pregnant women and found bread fortification alone was unsuccessful in preventing iodine deficiency during pregnancy[13]. In a UIC study undertaken in Sydney, the researchers found that a cohort of pregnant women in their third trimester were mildly iodine deficient[15]. A recent iodine study in pregnant women from the Illawarra region of New South Wales found the participants to be mildly iodine deficient (median UIC 87.5 µg/L) and only 14.5% of the participants had an adequate UIC of ≥150 µg/L[8]. That study also found 15% of pregnant women had a UIC <50 µg/L.

The Illawarra study is the only other Australian study to look at iodine knowledge and practice in pregnant women and our findings are similar to that study. In the Gippsland region, the food intake pattern of pregnant women for foods known to be a good source of iodine was poor. Of the foods containing good sources of iodine, only milk, milk products and fortified bread were consumed regularly. In addition, the Gippsland study subjects were poorly informed about the importance of iodine in the diet, especially during pregnancy, as only one third of the respondents had heard of the importance of iodine during pregnancy of the importance of folic acid. In our unpublished paper on environmental iodine levels in Gippsland we found that the water iodine concentration in the Gippsland region (from reticulated tap water and rain water tanks) was negligible and was indicative of environmental iodine deficiency[16]. The majority of our study particicpants (>84%) reported drinking local tap/tank water and as a result drinking water would not be a useful dietary source of iodine. Their iodine intake from local tap water would be close to zero and not the 5-9% reported in the Australian Total Diet Study[10].

Clearly knowledge about the crucial importance of iodine in the diet, especially for pregnant and breast feeding women, is in urgent need of improvement. According to the United Nations declaration (1989, New York) every mother has the right to adequate iodine nutrition to ensure the newborn baby's normal brain development[17]. Our study is in agreement with the earlier Tasmanian study in suggesting that iodine fortification of bread (at the current level) is insufficient to prevent iodine deficiency in pregnant women[13]. Pregnant women in Gippsland should have access to effective iodine education programs and encouraged to either consume iodine rich foods or take appropriate iodine supplements to improve their iodine status during pregnancy. We also suggest that greater efficacy would result from the use of iodised salt in all processed food as well as in bread products.

Acknowledgements

The authors gratefully acknowledge all the pregnant women from the Gippsland region who participated in our study. They also thank all the midwives, nurses, hospital staff, medical officers, obstetricians, general practitioners and administrative staff who were involved in this study. We also thank G. Ma, M Li and C. Eastman for assistance in carrying out the urine iodine concentration assays.

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CHAPTER 7

Integrated discussion

The lack of the essential micronutrient iodine is a risk factor for many health problems including impaired intellectual development. The World Health Organization rates Australia as iodine deficient and in response Food Standards of Australia and New Zealand (FSANZ) have introduced a national iodine supplementation program via the fortification of bread products. This program takes no account of state or regional differences or of the increased need for iodine during pregnancy. Yet the National Iodine Nutrition Study (NINS) showed that Victoria had the worst level of iodine deficiency in Australian school children. And Gippsland has a long and well documented history of iodine deficiency. Despite these indications of local differences regions are not screened and the need for iodine during pregnancy is not well understood by families or health professionals. In response to the public health aspects of this problem we devised and carried out a four part study to research a regions iodine status using Gippsland as a case study.

The thesis used a variety of methods to research (1) archival material on the history of iodine and iodine supplementation in Gippsland; (2) test the water iodine concentration in Gippsland water; (3) test the population iodine status of Victorian newborns using retrospective analysis of newborn heel prick test results and (4) measure the urinary iodine status and diet of a cohort of Gippsland pregnant women. All four studies indicate that dietary iodine deficiency is a public health problem in Gippsland and Victoria.

The first objective of this study was to examine the historical evidence of dietary iodine deficiency in Gippsland. Paper 1 reviewed the available data on this objective. We found clear historical evidence of regional iodine deficiency in Gippsland. This indicated that taking an effective history is vital to planning all health interventions. We found that depending on data available on electronic databases was not sufficient. A meticulous search of archival material and information from the local population can aid in finding key historical data that can support better health care in general and a better iodine supplementation policy in particular. In line with WHO recommendations Government and health authorities should undertake regular iodine status monitoring in regions with a history of iodine deficiency. Despite our work the history of dietary iodine deficiency in Gippsland is incomplete. More detailed historical research is needed to complete the picture.

The second objective was to research the environmental iodine status of the Gippsland region. Paper 2 confirmed that iodine concentrations in Gippsland water is consistent with environmental iodine deficiency and significantly different from the average iodine concentration of Australian tap water as described in the 22nd Australian Total Diet Study. Gippsland water contributes a negligible source of iodine for the local population. Food Standards Australia and New Zealand (FSANZ) should amend the assumptions of the daily dietary contribution of water as a source of iodine for environmentally iodine deficient regions such as Gippsland. Our findings also indicate that regional variations in iodine levels should be taken into account while calculating the contribution of different dietary iodine sources as foods grown in iodine deficient soil will have low iodine concentrations. Milk and milk products are known to be the major dietary source of iodine in the Australian diet. Regional variations need to be confirmed in these foods to obtain a fuller picture on all sources of iodine. Moreover, there is an urgent need for a region wide population iodine status assessment and appropriate dietary iodine supplementation program that takes regional differences into account.

The third objective was to estimate the population iodine status and factors affecting it. Both paper 3 and paper 4 provide information on this objective. Paper 3 focused on developing a cost effective and appropriate method to regularly monitor population iodine status using retrospective analysis of the neonatal TSH values. This is a novel approach. Our data analysis indicates that newborn babies in Gippsland and Victoria as a whole are iodine deficient and at increased risk of irreversible brain damage and a lowered IQ. Furthermore, this iodine deficiency in newborns clearly indicates inadequate intake of iodine during pregnancy. This excellent proxy indicator of population iodine status should become part of the regular neonatal screening program in Australia. This method also can aid in assessing the effectiveness of the current bread fortification program. A grant application has been made to the National Health and Medical Research Council (NHMRC) to use this monitoring method Australia wide.

Paper four measured the iodine status of a cohort of Gippsland pregnant women before and after the Food Standards of Australia and New Zealand (FSANZ) national bread iodine fortification program. The median urine iodine concentration in this cohort indicates inadequate iodine intake during pregnancy and that the national bread fortification has not delivered an adequate amount of iodine for pregnancy. There should be an urgent consideration of adding a component to the national iodine fortification program that can improve both knowledge about the importance of iodine and lead to increased iodine intake during pregnancy. This part of the study looked at the impact of initial phase of the bread fortification program on a small number of Gippsland pregnant women. Urine sample collection on a larger sample size in other parts of Australia will provide a better understanding of efficacy of the current bread fortification program. The pregnant mothers' urine samples were collected in the third trimester but could not be correlated with the respective newborn babies TSH value and urinary iodine level. That would give a better understanding of the relationship between maternal and foetal iodine deficiency.

Contribution of the thesis to evidence based knowledge

When these sub studies are analysed together they prove the hypothesis that there is a recurrence of dietary iodine deficiency in the Gippsland region. They address all of the research objectives which were 1. To examine the historical evidence of dietary iodine deficiency 2. To research environmental iodine status. 3. To estimate the population iodine status and factors affecting it.

The sub studies contribute to local, national and international knowledge of iodine deficiency in the following ways:

1. Taking a history and applying the lessons learnt is vital to ensure effective public health policy and practice. History needs to be considered locally, sub regionally, regionally, nationally and internationally.

2. The environment is also vital. Gippsland is environmentally iodine deficient and significantly different from other areas of Australia. Averaging water iodine levels to a national figure will not work. Iodine concentrations need to be monitored by water suppliers.

3. The retrospective neonatal TSH data analysis is a novel and cost effective approach to monitoring population iodine status. This method can be used to assess the effectiveness of supplementation programs such as the bread fortification program. Ours is the largest study of its kind in Australia and ranks among the biggest studies conducted worldwide. A future nationwide study is planned using this methodology.

4. The urine iodine study with a cohort of Gippsland pregnant women is the first study of its kind following the implementation of the nationwide bread iodine fortification. We found that the bread fortification program is unlikely to meet the iodine requirements of pregnancy. This is also among the few studies conducted in Australia that collected information on iodine nutrition during pregnancy. Given the lack of knowledge about iodine among the pregnant women who participated in our study we recommend a national information program be rolled out to health professionals and to pregnant women.

Conclusion

Iodine deficiency is a recognised public health problem in Australia . What is less well known is both the long history of iodine deficiency and the regional differences in environmental iodine across Australia.This comprehensive study is unique because of its focus on Gipplsand , its recommendation about the importance of taking an effective history and implementing the findings, its innovative use of TSH monitoring and its timing which enabled the comparision of pre and bread fortification data. Future research that follows on from this thesis should include a national TSH study, research on intellectual performance due to the effect of iodine deficiency and the continued improvement of the history of iodine.

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APPENDICES

Poster

Gippsland Iodine Study

Can you help?

Iodine is a micronutrient that is essential for healthy development of babies. Recent studies suggest that Australia is an Iodine deficient country and pregnant women may be suffering from iodine deficiency. Gippsland has a history of iodine deficiency and there is no available information on the dietary iodine status of pregnant women in the Gippsland region. Therefore we are undertaking a study in different antenatal clinics in Gippsland.

If you are

- Over 18
- And are at 28 or more weeks of pregnancy
- And not taking any thyroid hormone supplementation (eg, thyroxine)

Then you may want to help with our study.

This will involve providing a morning urine sample and filling in a pregnancy dietary habit questionnaire.

Please contact reception at _________ clinic for a research kit that you can return on your next visit.

Whether you choose to participate in the study or not if you have any question about iodine deficiency please seek the advice of your doctor.

For more information with the study you may contact
Dr. Ashequr Rahman
Monash University Department of Rural and Indigenous Health.
3 Ollerton Avenue, Moe, VIC-3825
Phone: (03) 51281000

Explanatory Statement

MONASH University

15/07/08

Explanatory Statement

Title: Dietary iodine insufficiency among pregnant women in the Gippsland region

This information sheet is for you to keep.

My name is Ashequr Rahman and I am conducting a research project with Assoc Prof Janice Chesters and Dr Gayle Savige in the Monash University Department of Rural and Indigenous Health and Dr. Nick Deacon and Dr. Barbie Panther in the School of Applied Science and Engineering towards a PhD. This means that I will be writing a thesis which is the equivalent of a short book/several magazine articles.

Why this research has been undertaken?
Micronutrients are substances which are essential to maintain normal functioning in our body. Iodine is a micronutrient and it is required in larger amounts during pregnancy to ensure the healthy development of the baby. Recent studies suggest that Australia is an Iodine deficient country and pregnant women may be suffering from iodine deficiency. Gippsland has a history of iodine deficiency and there is no available information on the dietary iodine status of pregnant women in the Gippsland region. Therefore we are undertaking a study in different antenatal clinics in Gippsland.
Your health agency has given us permission to ask you to participate in this research project.

The aim/purpose of the research
- Exploring the extent and distribution of iodine insufficiency among pregnant women in Gippsland.
- Establish a baseline to test/monitor the effectiveness of the proposed national iodine fortification scheme.
- Strengthen advocacy for effective iodine supplementation if iodine deficiency is established.

Possible benefits
This project will provide valuable information for maternal and child heath in Gippsland and will contribute to national public health policy.

What does the research involve?
The filling in of a questionnaire and the provision of a urine sample. The questionnaire will be matched with the result of the urine sample.

How much time will the research take?
It will take approximately 10 minutes to complete the questionnaire. You will also be provided with a urine sample collection bottle to collect a sample of your morning urine.

Inconvenience/discomfort
Mild level of inconvenience to the participant might occur by providing a urine sample and filling in the questionnaire.

Inclusion/ Exclusion criteria:
Inclusion : Pregnant women aged 18 or over at 28 week gestation or over
Exclusion : 1. Pregnant women taking thyroxine tablet will be excluded. Thyroxin is a thyroid hormone supplementation which may bias the results.
2. Pregnant women under the age of 18 years.

Payment
No form of payment or reward, financial or otherwise will be offered. However, health education material on Iodine will be provided to the participants.

Can I withdraw from the research?
This study is voluntary and you are under no obligation to participate. However, if you do consent to participate, you may only withdraw prior to the urine sample and questionnaire being submitted.

Confidentiality
The data will be collected anonymously. A unique code will be provided to each participant to maintain confidentiality. Only researchers involved with this project will have access to the database.

Storage of data
Storage of the data collected is in line with University regulations. All data will be kept on University premises in a locked cupboard/filing cabinet for 5 years. The electronic data will be kept on a password protected computer. If no longer required, the data will be destroyed after this period.The urine samples may be stored for a maximum period of 5 years depending on the availability of proper storage; otherwise the samples will be destroyed after testing. A report of the study will be submitted for publication, but individual participants will not be identifiable in such a report.

Results
The urine analysis for the iodine level measurement is not a diagnostic test for dietary iodine deficiency, because it reflects your eating habits over the last 24 hours. It is however a very good measure of iodine levels in the Gippsland population. As this is a population survey, no individual result will be published. If you would like to be informed of the aggregate research finding, please contact Dr. Ashequr Rahman on **03-5128100** or ashequr.rahman@med.moansh.edu.au. Your doctor also will be informed about the research finding. However, the urine analysis will be performed in a research laboratory and may take some time to be completed.

If you have any question about iodine deficiency please seek the advice of your doctor.

If you would like to contact the **researchers** about any aspect of this study, please contact the Chief Investigator:	If you have a **complaint** concerning the manner in which this research is being conducted, please contact:
Assoc. Prof. Janice Chesters janice.chesters@med.monash.edu.au **Tel : +61 3 51281009** **Fax: +61 3 51281080**	Executive Officer, Human Research Ethics Standing Committee on Ethics in Research Involving Humans (SCERH) Building 3e Room 111 Research Office Monash University VIC 3800 Tel: +61 3 9905 2052 Fax: +61 3 9905 1420 Email: scerh@adm.monash.edu.au **IMORTANT:** For projects in non-English speaking countries, a local person who is also fluent in English must be nominated to receive complaints and pass them onto SCERH. Please replace above section (in blue) with the details of that person.

Thank you

Ashequr Rahman

Consent Form - Collection of urine, identifiable questionnaire and for use of data in future iodine research projects

Title: Dietary iodine insufficiency among pregnant women in the Gippsland region

NOTE: *This consent form will remain with the Monash University researcher for their records*

I agree to take part in the Monash University research project specified above. I have had the project explained to me, and I have read the Explanatory Statement, which I keep for my records. I understand that agreeing to take part means that:

1. I agree to provide one sample of urine
2. I agree to complete a questionnaire asking me about dietary iodine intake in relation to current and previous pregnancies
3. The information I provide can be used in future iodine research projects which have ethics approval as long as my name and contact information is removed. ☐ Yes ☐ No

I understand that my participation is voluntary, that I can choose not to participate in part or all of the project, and that I can withdraw up to the point where the urine sample and questionnaire has ben returned to the researcher without my healthcare being penalised or disadvantaged in any way.

I understand that data from the tests will be kept in a secure storage and accessible to the research team. I also understand that the sample will be destroyed immediately after analysis or after a 5 year period (if adequate preservation space is available).

Participant's name

Signature

Date

Questionnaire

For office use
Site
ID number

Questionnaire

Date Postcode Age (in years) Ethnic origin

Questions for eligibility to participate in the study:

A. Is your age below 18 years?

Yes ☐
No ☐

B. Are you taking any prescribed thyroid hormone supplementation?
(the common thyroid hormone preparations are Oroxin (thyroxin Sodium), Eutrosxig (thyroxin Sodium), Tertroxin (Liothyronin Sodium) etc and you may check the name written on the pack or bottle)

Yes ☐
No ☐

C. Are you at less than 28 weeks gestation?

Yes ☐
No ☐

If you have answered yes in either A or B or C or then you are not eligible to participate in this study. If your answer is no in A,B and C then you are eligible to participate in this study. In that case, please proceed to question 1.

1. How often do you eat the following foods during this pregnancy:

Food items	Daily	2-3 times/week	Weekly	Monthly
Table salt				
Cooking salt				
Seafood				
Seaweed (eg.Californian rolls, Nori Wraps, Miso, Seaweed Biscuit etc)				
Sushi				
Milk				
Milk products (eg. cheese, yogurt etc)				
Eggs				
Bread				

1a. If you eat bread, please tell us the number of slices you eat on an average day
..............slices of bread

1b. Do you use iodised salt

Yes ☐
No ☐
Don't know ☐

2. Are you currently taking any supplements (eg multivitamin tablets)?

Yes ☐
No --------------------go to Q 4

3. Please answer the following questions regarding supplements.

a) Brand name of supplements: please tick the name from the following list:

Accomin	
Aussie Women's Multivitamin tablets	
Blackmores pregnancy and breastfeeding Gold	
Centrum	
Clement's oral iron liquid	
Mannatech-Ambrotose	
Natural nutrition mega potency women's multi	
Neways Oracle	
N/Way Pregnancy multivitamin	
Microgenics pregnancy multivitamin w.tuna oil	
Swiss women's ultivite formula 1	
Vitelle multivitamin	
Others (please mention)........................	

b) Tablets taken in a day

1 ☐
2 ☐
more than 2 ☐

c) Started taking these tablets

Before pregnancy ☐
During pregnancy ☐

d) If started during pregnancy, please mention the week you started taking those tablets:

Weeks of pregnancy ☐☐

e) Who advised you to take the tablets?

Doctor ☐
Pharmacist ☐
Self ☐
Others (Please list)................☐

4. Do you consume home grown vegetables?

Daily ☐
2-3 times/week ☐
Weekly ☐

4a. Do you consume home grown fruit?

Daily ☐
2-3 times/week ☐
Weekly ☐

4b. Have you heard about the importance of taking folate during pregnancy?

Yes ☐
No ☐

5. Have you heard about the importance of taking iodine during pregnancy?

Yes ☐

If yes, what was the source of your information:
GP/ Primary health care provider ☐
Specialist ☐
Pharmacist ☐
Web sit ☐
Other pregnant women ☐
Others (Please list)………………. ☐

No ☐
Not sure ☐

7. What is the main source of your drinking water?

Mains tap water ☐
Rain water tank ☐
Bottled water ☐
Others (please list)……….. ☐

7a. Have you lived mainly in the Gippsland region during your current pregnancy?

Yes ☐
No ☐

Now we want to talk about your previous pregnancies that resulted in the birth of a live baby.

8a. Number of live births: ☐

8b. Did you live mainly in the Gippsland region during those pregnancies:

Order of pregnancy	Yes	No
During pregnancy 1		
During pregnancy 2		
During pregnancy 3		

8c. Can you remember which of the following items you consumed in those pregnancies as compared to the current pregnancy

Food items	Consumed similar amount	Consumed more amount	Consumed less amount	Did not consume	Can't remember
Table salt					
Cooking salt					
Seafood					
Seaweed (eg.Californian rolls, Nori Wraps, Miso, Seaweed Biscuit etc)					
Sushi					
Milk					
Milk products (eg. cheese, yogurt etc)					
Eggs					
Supplements (eg Multivitamin tablets)					

8d. Did you use iodised salt in those pregnancies?

Order of pregnancy	**Yes**	**No**	**Can't remember**
During pregnancy 1			
During pregnancy 2			
During pregnancy 3			

9. Please tell us about any changes in your eating habits during this pregnancy.

10. Please tell us about any changes in your lifestyle (including smoking and drinking) during this pregnancy.

ERRATA

p 3 line 12: change of font size

p 5 lines 17-19: Following words deleted: Years, Intervention, Area

p 6 lines 4-14: Following words deleted: Water treatment plant location, Distance from the sea (Km), Untreated water iodine concentration (µg/L), Treated water iodine concentration (µg/L), Location, Distance from the sea (Km), Water Iodine concentration (µg/L), Age group, Mean lower bound intake (µg/day), Percent contribution of water to total intake of iodine, Calculated amount of Iodine received from Australian tap water (µg/day).

p 15 line 5: "Total" for "total"

p 17 line 21: "iodine" for "Iodine"

p 25 line 2: "The data were.." for "The data was.."

p 27 line 29: font size changed

p 30 line 5: ";" deleted

p 34 line 26: "...it contained were..." for "...it contained was..."

p 36 line 31: "Places with historical evidence…" for "Places with a historical evidence…"

p 37 line 22: "...neonatal population..." for "…Neonatal population…"

p 37 line 29: "So we sought…" for "So we wanted sought…"

p 44 line 2: "…1948-1965 to contact…" for "…1948-1965 contact…"

p 44 line 15: "…information from the archive and rare books was" for "…information from the archive and rare books were…"

p 46 line 16: "…concentration data were…" for "…concentration data was…"

p 48 line 3: "The data were…" for "The data was…"

p 48 line 4: "…then the data were…" for "…then the data was…"

p 48 line 25: "…criteria were followed…" for "…criteria was followed…"

p 50 line 14: "From Ante-natal…" for "…From Anti-natal…"

p 51 line 22: "The data were…" for "The data was…"

p 59 line 10: "…iodine tablets…" for "…iodine tablet…"

p 60 line 6: "…Food Standards…" for "Food Standards of…"

p 60 line 22: "…studies suggest that…" for "…studies suggests that…"

p 63 line 12: "…Clements's studies…" for "…Clements studies…"

p 64 line 6: "…children, and expecting…" for "…children, expecting…"

p 64 line 7: "…nursing mothers…" for "…nursing mother…"

p 64 line 17: space between "." and "Iodine"

p 65 line 3: "… survey data exist." for "…survey data exists."

p 65 line 5: "…iodine prophylaxis…" for "…Iodine prophylaxis…"

p 66 line 18: "iodine induced hyperthyroidism" for "Iodine induced hyperthyroidism"

p 69 line 10: "Most significantly, historical evidence…" for "Most significantly historical evidence…"

p 97 line 14: "…Lanka. The Science…" for "…Lanka The Science…"

p 99 line 13: "…as well as Victoria…" for "…as well Victoria…"

p 106 line 14: "database on iodine deficiency…" for "database on Iodine deficiency…"

p 109 line 6: "…96 hours after birth…" for "… after 96 hours of birth…"

p 113 line 6: "…as these data…" for "…as this data…"

p 113 line 9: "…included those blood samples which …" for "…included the blood samples those…"

p 115 lines 1-11: aligned with line 12

p 116 line 5: space deleted between "information" and "system"

p 136 line 8: "Yeatman H et al" for "Heather Yeatman et al"

p 142 line 2: "…recommendations government…" for "recommendations Government"

p 149 line 23: "Network for Sustained Elimination of Iodine deficiency. Global Scorecard 2010. Ottawa, Canada June 2010. www.iodinenetwork .net/documents/scorecard-2010.pdf" for "www.iodine network.net/documents/scorecard-2010.pdf"

p 150 line 11: "Australian and New Zealand Journal of Public Health…" for "Australian And New Zealand Journal Of Public Health…"

p 150 line 14: "…Journal of Clinical Nutrition…" for "…Journal Of Clinical Nutrition…"

p 150 line 20: "Medical Journal of…" for "The Medical Journal Of…"

p 150 line 24: "Medical Journal of Australia 2006" for "Med J Aust 2006"

p 150 line 27: "Journal of the American" for "Journal Of The American"

p 150 lines 31-32: "Medical Journal of Australia 2006" for "The Medical Journal Of Australia 2006"

p 151 line 5: "…by ethnic group. Asia Pacific Journal of…" for "…by ethnicgroup. Asia Pacific Journal Of…"

p 151 lines 9-10: "Medical Journal of Australia 2007" for "The Medical Journal Of Australia 2007"

ADDENDUM

1. p 43: add at the beginning of para 2: "Used qualitative research methods to…"

2. p 43: add at the beginning of para 4: "The initial information obtained from archival research did not establish the exact areas where iodine tablets were distributed so we devised a press release to seek community information on the topic."
3. p 43: delete at the beginning of line 2: "Later, we devised a press release that…" and add: "The press release…"

4. p 44: add at the end of para 2: "The inclusion criteria included the history of the prevention of iodine deficiency in Gippsland and Victoria as well as Australia as a whole and relevant iodine status monitoring studies. Six journals articles/ Government archival documents were found to be relevant. They provided an insight into the forgotten history of iodine deficiency in the Gippsland region."

5. p 44: add at the beginning of para 3: "The qualitative research method used was historical research[38, 39]. These included cross checking sources, establishing the location of archive, textual analysis and emphasis on using primary sources (by asking Gippsland population about their exposure of taking iodine tablets)."

6. p 45: add at the end of line 18: "Gippsland Water is the major water supplier in the Gippsland region (it has a total of 17 water treatment plants) and supplies all Gippsland shires (Latrobe, Baw Baw, East Gippsland, South Gippsland, Wellington and Bass Coast). Westernport Water has only one water treatment plant. We sampled all 18 water treatment plants of the two water service providers who agreed to assist in our study."

7. p 45: add at the end of line 25: "Initially our intention was to extensively test the iodine level of rain water tank in a similar way to the treatment plant study and we applied for a grant to do this work. However, the grant application was not successful and we therefore collected and tested a smaller number of water samples with in kind support. Both Gippsland Water and Westernport Water provided assistance in the collection of water samples from their treatment plants. We were able to collect rain water tank samples from Monash staff members who lived in three shires (Baw Baw, Latrobe and South Gippsland) that were located at different distances from the sea (30 to 70 km)."

8. p 49: add at the end of line 9: "The Gippsland region is divided into six Local Government Areas (LGA) and the seven hospitals/ clinics surveyed are the main centres for regular ante-natal classes in those shires. Choosing those hospitals provided the opportunity to obtain urine samples from all major sites across the Gippsland region. A few, very small antenatal clinics were not included in the study as the women attending these clinics were often referred onto the major antenatal clinics."

9. p 51: add at the end of line 13: "The main objective of the short dietary questionnaire was to focus on the women's intake of a few key foods containing iodine, the self reported use of supplements and the estimated intake of bread.

   The questionnaire was pilot tested among some volunteer women to check the accuracy, understanding and the length of time needed to complete the questionnaire.

   While we acknowledge this was a less than perfect study the survey results supported the results of the urinary analysis. As foods containing good sources of iodine are very limited it was assumed that most people would be able to say with sufficient accuracy the amount of bread, milk, fish they ate and whether or not they used iodised salt. Bread is a staple for the majority of Australians of anglo-celtic ethnicity (and >93% of our survey population were of anglo-celtic origin). The responses were firstly entered into Microsoft Access database and later converted into a suitable SAS format. These data were analysed according to the objectives of the urinary iodine study."

10. p 51: add at the end of line 23: "…and analysed according to the objectives of the urinary iodine study."

11. p 51: add at the end of line 10: "The reasons for collecting the morning urine samples were for the convenience of the women. The women could collect the sample in the comfort of their home environment and then deliver the samples at the beginning of the ante-natal class. It also helped not to disrupt the regular activities of an ante-natal class.

    According to the ethics protocol, the purpose and procedure involved in the urinary iodine study was explained to pregnant women in ante-natal clinics. Those who agreed to participate were supplied with a urine sample collection kit and questionnaire and were asked to return these at their next visit to the ante-natal clinic. However, it was common for some of the pregnant women to forget to return with the urine sample at their next visit and so these women were asked for a spot sample. World Health Organization (WHO) suggests that there is no problem with analysing urinary iodine levels from morning or casual samples[8]."

12. p 152: add reference: 38. Denzin NK. The Research Act. New York. McGraw Hill. 1978.

13. p 152: add reference: 39. Denzin NK, Lincoln YS eds. Hand Book of Qualitative Research. Thousand Oaks, Sage publications. 1994.