AN INVESTIGATION OF THYROID HORMONE LEVELS AND DISEASE IN NEW SOUTH WALES CHILDREN

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AN INVESTIGATION OF THYROID HORMONE LEVELS AND DISEASE IN NEW SOUTH WALES CHILDREN

by

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Submitted as part of course requirements for the

Master of Community Health (by Coursework) degree

School of Community Health

Faculty of Health Sciences

The University of Sydney

Wednesday, November 30, 1994

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ACKNOWLEDGEMENTS

I wish to express my sincere thanks and appreciation to the following people without whom the completion of this treatise would not have been possible -

Dr. John Coakley, Department Head, Clinical Biochemistry Department, Royal Alexandra Hospital for Children, whose willingness to allow the research to take place within the department, often out of hours, is greatly appreciated. His timely advice, expertise and assistance with the project is much appreciated.

Dr. John Earl, Developmental Biochemist, Clinical Biochemistry Department, Royal Alexandra Hospital for Children, who as a co-supervisor on the project, freely offered much of his own time and expertise throughout the entire project. His support and encouragement throughout the completion of this treatise are also greatly appreciated.

Dr. Kaye Brock, School of Community Health, Faculty of Health Sciences, University of Sydney, who as a co-supervisor on the project, offered much guidance and advice, especially throughout the final stages of the project.

Mr. Rogan McNeil, Statistician, Royal Alexandra Hospital for Children, whose expertise and advice on the use of appropriate statistical methods and interpretation of the results of the project are greatly appreciated.

Finally, thank you to the staff and students of the School of Community Health and other departments of the Cumberland College of Health Sciences, University of Sydney, and to my family and friends for their support throughout this project and the entire degree.

Anna Agnos

ABSTRACT

This epidemiological study investigated the proposed relationship between three parameters of thyroid function - thyroxine (T_4), triiodothyronine uptake (T_3U) and thyroid stimulating hormone (TSH), and various diseases in a population of N.S.W. children of varying age, who underwent blood screening for thyroid function at the Royal Alexandra Hospital for Children between 1980 and 1990. Age, sex, puberty and year of diagnosis were identified as potential confounders in the study and various measures taken to control for these factors in the analysis. The study population was divided into two broad categories: patients aged less than 3 years of age and, patients aged 3-18 years of age. The main analysis concentrated on the 3-18 year age group. A Short Stature diagnostic group was selected as a control group in this category. As the diagnostic groups identified varied in normality, the Wilcoxon Rank Sum Test was used for significance testing of the data. Seventy-eight separate diagnostic groups were identified in patients aged 3-18 years. Twenty-one diagnostic groups showed a statistically significant mean difference ($p < 0.05$) for T_4 between the cases and the control group. Of these, the following diagnostic groups were selected for analysis and found to have a significantly *low* T_4 compared to the control group: Selected Diabetes, Thalassaemia, Growth Hormone Deficiency, Anorexia Nervosa, Acute Lymphoblastic Leukaemia, various Psychological disorders and Cystic Fibrosis. The following diagnostic groups were found to have a significantly *high* T_4 compared to the control group: Obesity, Deafness, Failure to Thrive, Slipped Epiphyses, Turner's Syndrome and Juvenile Chronic Arthritis. These groups were stratified by sex and puberty (3-11 years and >11-18 years) and similarly analysed. A further analysis was performed in order to produce an odds ratio. These diagnostic groups seemed to affect thyroid function in either of three different ways. Conditions affecting the thyroid gland directly were reflected in the results for T_4. Conditions affecting protein binding mechanisms were reflected in the results for T_3U and conditions which affect the hypothalamic-pituitary axis were reflected in the results for TSH. The literature generally supported the findings of this study.

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INTRODUCTION

Between 1980 and 1990, the results of thyroid testing of patients at the Royal Alexandra Hospital for Children (RAHC) in Camperdown, Sydney were recorded in a log book by Ms. Mary O'Halloran and occasionally Mrs. Fay Wood who performed the thyroid function tests during this period. These data included: the date of the sample, patient name, diagnosis, whether or not the patient was on treatment at the time and values for thyroxine (T_4), triiodothyronine uptake (T_3U) and thyroid stimulating hormone (TSH) on patients of varying age. The information was stored using an alphabetical system so that all patients whose surnames began with the letter "A" were stored in the "A" section of the log book and so on. The information in the log book became the basis of this epidemiological study. These data were then entered onto a computerised database according to pre-determined criteria and analysed using varying statistical methods.

AIM

The aim of this study was to investigate the relationship between thyroid hormone levels and various diseases in a population of N.S.W. children who underwent blood screening for thyroid function but who were subsequently shown not to have thyroid disease. Seventy-eight separate diagnostic groups were identified in patients aged 3-18 years. Of these, the main diseases investigated were Short Stature, Selected Diabetes, Thalassaemia, Growth Hormone Deficiency, Anorexia Nervosa, Acute Lymphoblastic Leukaemia, various Psychological disorders, Cystic Fibrosis, Obesity, Deafness, Failure to Thrive, Slipped Epiphyses, Turner's Syndrome and Juvenile Chronic Arthritis.

CHAPTER 1

BACKGROUND

The General Role of Thyroid Hormones

The thyroid gland secretes tetraiodothyronine or thyroxine (T_4) and small amounts of triiodothyronine (T_3). The thyroid hormones have three principal effects on the body:

a) regulation of metabolism,

b) regulation of growth and development, and

c) regulation of the activity of the nervous system *(Tortora & Anagnostakos, 1987)*.

With respect to regulation of metabolism, the thyroid hormones stimulate virtually all aspects of carbohydrate and lipid metabolism in most cells of the body. They also increase the rate of protein synthesis. The thyroid hormones also help to regulate tissue growth and development, especially in children. Deficiency of the hormones during foetal development can result in fewer and smaller neurons, defective myelination of axons and mental retardation. During the early years of life, deficiency of the hormones results in short stature and poor development of certain organs and is required for normal growth and maturation in children *(Wyngaarden, & Smith, 1988)*. The thyroid hormones also increase the reactivity of the nervous system which results in increased blood flow, increased blood pressure, increased motility of the gastrointestinal tract and increased nervousness.

Regulation of Thyroxine Levels in the Blood

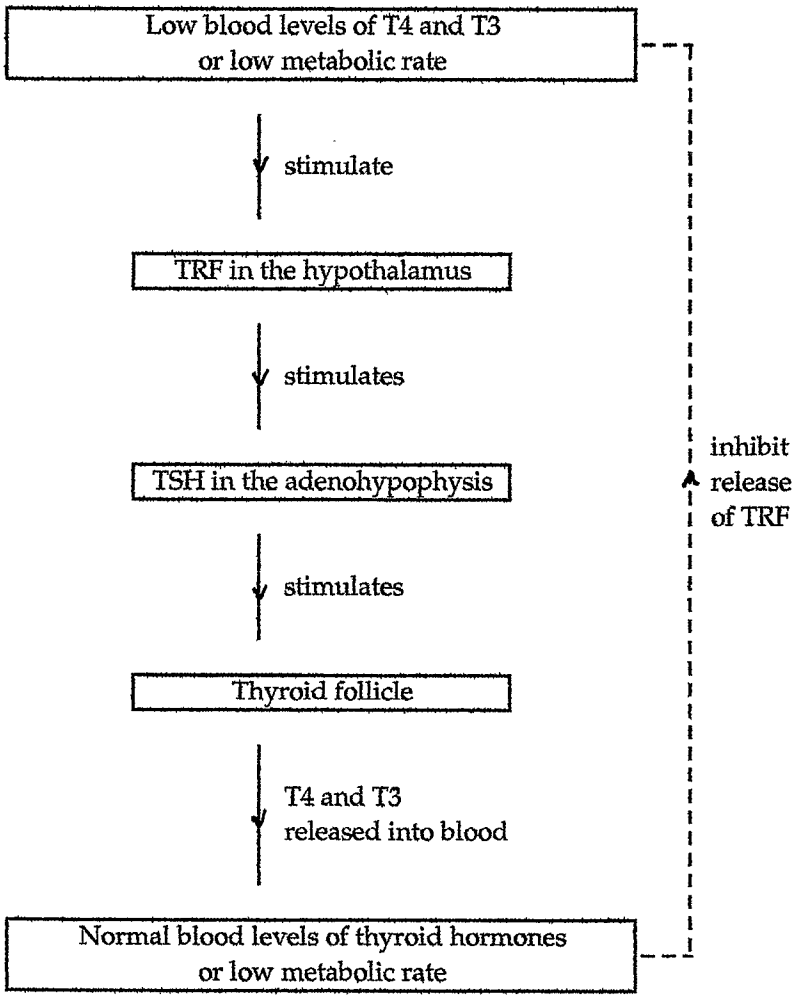
The normal thyroid gland produces about 85 micrograms of T_4 daily, with the normal range for T_4 being 65-180 nmol/L (> 3 years of age). About 80 per cent of T_3 is produced from conversion of T_4 to T_3 in peripheral tissues. The remaining 20 per cent of T_3 arises from direct thyroid gland secretion *(Middlesworth, 1986)*. The regulation of the secretion of thyroid hormones is shown in Figure 1.1 and is stimulated by several factors. If T_4 levels in the blood fall below normal, or the metabolic rate decreases, chemical sensors in the hypothalamus which monitor the

levels of T_4 in the blood, stimulate the hypothalamus to secrete thyrotropin releasing factor (TRF), a regulating factor. TRF acts on the pituitary gland to secrete thyroid-stimulating hormone (TSH) into the blood. TSH then stimulates the thyroid to release thyroid hormones until the metabolic rate returns to normal. Conversely, if T_4 levels in the blood are high, then TRF production is reduced which leads to reduced TSH and subsequent lowering of T_4 until blood levels return to normal.

Conditions that increase the body's need for energy - a cold environment, high altitude, pregnancy - also trigger this feedback regulatory system and increase the secretion of thyroid hormones. Thyroid activity can be inhibited by a number of other factors including large amounts of circulating oestrogens, other sex hormones, and ageing *(Tortora & Anagnostakos, 1987)*.

Thyroid hormones in plasma exist in two forms, free and protein bound. Although only about 0.02 per cent of total plasma T_4 and 0.3 per cent of plasma T_3 are free, it is the free hormone concentration that is maintained constant by the feedback regulatory system and that appears to parallel the rate of cellular uptake of these hormones. *(Wyngaarden, & Smith, 1988)*. It is, therefore, the free hormone concentration that determines the thyroid status irrespective of the total plasma concentration. The delivery system for the thyroid hormones includes a set of circulating transport proteins that vary widely in concentration and affinity for thyroid hormone *(Robbins, cited in Braverman & Utiger, 1991)*. The net result is more than 99 per cent of the circulating hormone is protein-bound but can be liberated with great rapidity for entry into cells. Thyroid-binding globulin (TBG) is responsible for much of the immediate delivery of T_4 and T_3 into the cells and carries about 70 per cent of the circulating T_4 and T_3 by virtue of its high affinity. It has no other known physiological function *(Robbins, cited in Braverman & Utiger, 1991)*. Other plasma proteins carrying thyroid hormones are albumin and transthyretin, but to a much lesser extent than TBG.

Figure 1.1 **Regulation of the secretion of thyroid hormones**



(adapted from Tortora & Anagnostakos, 1987)

Measurement of Thyroid Hormone

Measurements of total thyroid hormone concentrations utilize radioimmunoassay (RIA) techniques and measure both bound and free hormones. These include measurements of T_4 and T_3. The similar binding characteristics of T_4 and T_3 allow the calculation of a free T_4 and free T_3 index from the product of the T_3 uptake ratio (T_3U) and total T_4 or total T_3. Results for T_3U measurement are not an indicator of T_3 directly, but of free T_4. The resulting free hormone index is effective in most clinical settings. The free hormone fraction can be measured directly, using equilibrium dialysis or ultrafiltration methods that utilize membranes that allow only free hormone to pass through. These methods are rarely needed for clinical diagnosis. Serum TSH is measured by RIA and may be the most sensitive indicator of thyroid status in nonthyroidal illness *(Middlesworth, 1986)*. At the RAHC, RIA was used for both T_4 and TSH measurement. T_3U was measured in a resin uptake test.

Serum Thyroid Hormone levels during Childhood

The variations in serum thyroid hormone and TSH concentrations during the first 20 years of life show serum T_4 and T_3 concentrations both decreasing gradually with age. Serum T_3U values remain relatively constant during childhood and adolescence, indicating that the free T_4 and free T_3 fractions are stable during this time. The free T_4 and free T_3 indices, however, decrease progressively, indicating a progressive decrease in free T_4 and free T_3 concentrations with age. The decreases with age in the ratios of T_3 to serum reverse T_3 (rT_3) and free T_3 index to free rT_3 index suggest a progressive decrease in the relative conversion of T_4 to T_3 with age during the first 15 years of life. *(Fisher, cited in Braverman & Utiger, 1991)*. The mechanism for the relative decrease in thyroid function is not clear as to whether it is mediated by a decrease in TSH secretion or a decrease in thyroid gland responsiveness with age, or both.

Clinical Conditions

Hypothyroidism

Although patients listed with a diagnosis of hypothyroidism have been excluded in this study, hypothyroidism is one of the most common disorders of thyroid function and therefore worth noting.

Hypothyroidism is most often due to decreased thyroid hormone production by the thyroid gland, known as primary hypothyroidism. It can also be due to decreased thyroidal stimulation by TSH, due either to pituitary disease or to diminished pituitary stimulation as a result of a deficiency of TRF. In this case it is known as central, or secondary hypothyroidism because the hypothalamic-pituitary axis (HPA) is affected. Tertiary hypothyroidism is a deficiency in TRF itself. The clinical features of hypothyroidism are largely independent of its cause. It affects both sexes and all ages, although the age of the patient and the presence of other diseases affect the clinical presentation of the disease. It may be overt or subclinical; the latter is most often defined as increased serum TSH and normal T_4 and T_3 concentrations, *(Braverman & Utiger, 1991).*

Generally, a paediatrician may request a thyroid function test on a child suspected of having a thyroid problem. Thus children who are short, slow growing or slow to develop etc., may be tested to ensure they do not have a thyroid-related condition such as hypothyroidism. Conversely, children who are overactive and tall, or rapid to develop are tested to ensure they do not have hyperthyroidism.

In some cases a thyroid problem is detected. The remaining children, for whom thyroid disease has been excluded, are then essentially normal children who happen to be at either extremes of height or weight when compared to the general population for their age, for reasons which may be unrelated to thyroid hormone control mechanisms. In this study, patients with known thyroid disease were excluded and

the remaining major disease groups were investigated to see if there existed any relationship between thyroid hormone levels and the diagnosis listed. Some of the main disease groups encountered are outlined below.

Short Stature

In adolescence, short stature is defined as a height greater than 2.5 standard deviations below the mean age for adolescence *(Cohen & Rosenfeld, 1992)*. This can have many causes, including multiple endocrine and systemic disorders. Of these, normal variants are by far the most common, with endocrine disorders accounting for only 10 percent of the cases of short stature *(Cohen & Rosenfeld, 1992)*. In a normal child of short stature, any of the following may be present: low birth weight, (particularly under 1000g), extreme prematurity, low mid-parental height, slight build of siblings or other close relatives, normal growth velocity, no lack of energy or responsiveness, observed normal interaction with parents and doctor, no symptoms or signs of poor intake, malabsorption, or excess output, *(Marcovitch, 1994)*.

Insulin-dependent Diabetes Mellitus

Insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes, is characterized by an absolute deficiency of insulin due to a marked decline in the number of insulin-producing beta cells in the pancreas, thought to be due to an autoimmune process. IDDM usually develops during childhood, the peak incidence occurring at puberty, *(Craighead, cited in Rubin & Farber, 1988)*. Some cases develop during the first years of life, and a fewer number develop after maturation. Fewer than 20% of IDDM sufferers have a parent or sibling with the disease, so environmental factors may play a role in the development of the disease *(Craighead, cited in Rubin & Farber, 1988)*.

Thalassaemia

The term thalassaemia represents a group of hereditary haemolytic anaemias, resulting from a defect in the synthesis of haemoglobin, which produces extremely thin and fragile erythrocytes *(Tortora & Anagnostakos, 1987)*. The severity of the resulting anaemia reflects both the degree of cell destruction and the decreased erythrocyte haemoglobin content. The specific thalassaemia syndromes are defined by the globin chain part of normal haemoglobin A that is affected. In alpha-thalassaemia, there is an abnormal synthesis of the alpha-chain, while in beta-thalassaemia, synthesis of the beta-chain is affected *(Bonner, cited in Rubin & Farber, 1988)*. The distribution of thalassaemia follows the malaria belt, and may be attributable to the fact that certain thalassaemias enhance resistance to malaria. Although the thalassaemia syndromes are found world-wide, specific forms occur with high frequency in certain populations - notably in Mediterranean and Oriental populations, with beta-thalassaemia and alpha-thalassaemia more common in these respective groups *(Nathan, cited in Beck, 1985)*.

Growth Hormone Deficiency

Growth hormone deficiency may be due to a number of causes including:
a) hypothalamic dysfunction, with impaired synthesis or secretion of growth hormone-releasing hormone (GHRH);
b) isolated growth hormone deficiency;
c) absent or low pituitary GH activity as a result of abnormal GH molecules, or
d) unresponsiveness of the target organ to GH *(Gould & Sommers, cited in Rubin & Farber, 1988)*.

The molecular mechanism by which thyroid hormone permits normal GH secretion is unclear. Retarded growth caused by hypothyroidism appears to result from deficient secretion of GH as well as from impaired action of GH. Decreased GH

secretion in hypothyroidism probably results from a direct effect of thyroid hormone deficiency on the pituitary itself and less likely from an effect on GHRH, *(Snyder, cited in Braverman & Utiger, 1991).*

Anorexia Nervosa

Anorexia nervosa is a disorder characterized by loss of appetite and altered eating patterns. The subconsciously self-imposed starvation appears to be response to emotional conflicts about self-identification and acceptance of a normal adult sex role *(Tortora & Anagnostakos, 1987).* The disorder is found predominantly in young females and is one of the numerous disorders associated with low T_3 syndrome. Abnormalities in TSH secretion also occur in anorexia nervosa. Reduced basal and stimulated serum TSH levels may be a consequence of increased serum cortisol levels or a decreased response to TRF, and the mechanisms underlying this phenomenon are complex *(Scanlon, cited in Braverman & Utiger, 1991).*

Acute Lymphoblastic Leukaemia

Acute lymphoblastic leukaemia (ALL) is a malignant, clonal disorder of the bone marrow lymphopoietic precursor cells. The cause is unknown. Typically, the onset is acute or subacute in a previously healthy child or, less commonly in the adult. It is predominantly a disease of childhood, 85% of all cases occurring in children. It is also the most common paediatric malignancy. In children, the incidence peaks between 3 and 6 years of age, with Caucasian males being most commonly affected. *(Bonner, cited in Rubin & Farber, 1988).* As a result of more effective therapy, an increasing proportion of children with the disease, now survive into adulthood and some will be affected by residual side effects from their anti-leukaemic therapy.

Radiation and chemotherapy are capable of producing endocrine sequelae, which include GH deficiency, disorders of pubertal onset, thyroid failure and hypothyroidism. Subtle primary hypothyroidism is relatively common in patients

with ALL, particularly in those who have been treated with craniospinal irradiation *(Pasqualini et al, 1991)*. In this study, patients who were listed as having radiotherapy were excluded, as were those on chemotherapy.

Psychological Disorders

For the purposes of this study, a number of disorders were grouped to make a single diagnostic group. A variety of severe psychiatric disturbances may be associated with transient alterations in serum thyroid hormone levels *(Spratt et al, 1982)*. Characteristically, they take the form of elevated serum total and free T_4, variable TSH and normal T_3 concentrations. This pattern is most often found in manic-depressive and other psychotic patients. Although the aetiology of these changes is not known, they may represent the effects of a brief period of excessive endogenous TSH secretion secondary to disturbed hypothalamic function, *(Braverman & Utiger, 1991)*.

Cystic Fibrosis

Cystic fibrosis is a systemic genetic disease that affects essentially all exocrine glands of the body and results in abnormal sweat electrolyte content and hyperviscous secretions in the pancreas, biliary tract, and bronchial tree. Cystic fibrosis is the most common clinically important autosomal recessive disorder in Caucasian children, having an incidence of 1 in 2000 live births in this group, *(Millard & Lemen, cited in McAnarney et al, 1992)*. More than 95 percent of cases have also been recorded in this group *(Damjanov, cited in Rubin & Farber, 1988)* and 5 percent of Caucasians carry the defective gene. Cystic fibrosis is also found in children of other backgrounds, including blacks and Hispanics, but is much less common in these groups.

Obesity

Obesity is defined as excess adiposity, that is, more than 25 per cent of body weight composed of fat in males and more than 30 percent in females *(Arden, cited in McAnarney et al, 1992)*. Little is known about the aetiology of obesity. There are probably many different causes, some of which may co-exist in a single individual.

Endocrine dysfunction can cause obesity. Hypothyroidism may be suspected when accompanied by depression and sluggishness, and severe hypothyroidism can lead to increased fat, but most of the excess bulk is actually oedema, which is lost with thyroid hormone replacement therapy *(Wyngaarden, & Smith, 1988)*. T_4 regulates the metabolism of lipids in the body and clinically low T_4 levels are often associated with high levels of cholesterol and lipids in the blood.

Failure to Thrive

"Failure to thrive" tends to be a descriptive term, not a diagnosis. There is no clear agreement on definition but it is most commonly defined as "when his or her growth fails to meet the potential for a child of that age" and " signs of developmental retardation and of physical and emotional deprivation such as apathy, poor hygiene, intense eye contact with people and withdrawing behaviour" as well as "disorders of oral intake which may be manifested as anorexia, voracious appetite or pica" *(Marcovitch, 1994)*. This description includes characteristics of psychosocial deprivation, eating disorders and poor growth, any combination of which may be present in an individual child.

Jaundice

An increased concentration of bilirubin in the blood (>0.01 mg/ml) is termed hyperbilirubinaemia. When the circulating bilirubin concentration attains levels greater than 0.02 mg/ml, the skin and sclerae become yellow and the condition is known as jaundice. Many conditions are associated with hyperbilirubinaemia. Over-

production of bilirubin, interference with hepatic uptake or intracellular metabolism of bilirubin, and impairment of bile excretion are all causes of jaundice *(Rubin & Farber, 1988)*. Jaundice appears often in neonates. The most obvious evidence of hepatic immaturity in neonates is the inability of the liver to conjugate and excrete bilirubin, leading to jaundice. It is more pronounced in premature babies and usually lasts longer in these infants than in those born at term. *(Rubin & Farber, 1988)*. Other liver functions are also not fully operational, but the deficiencies are easily overcome with adequate medical support.

Precocious Puberty

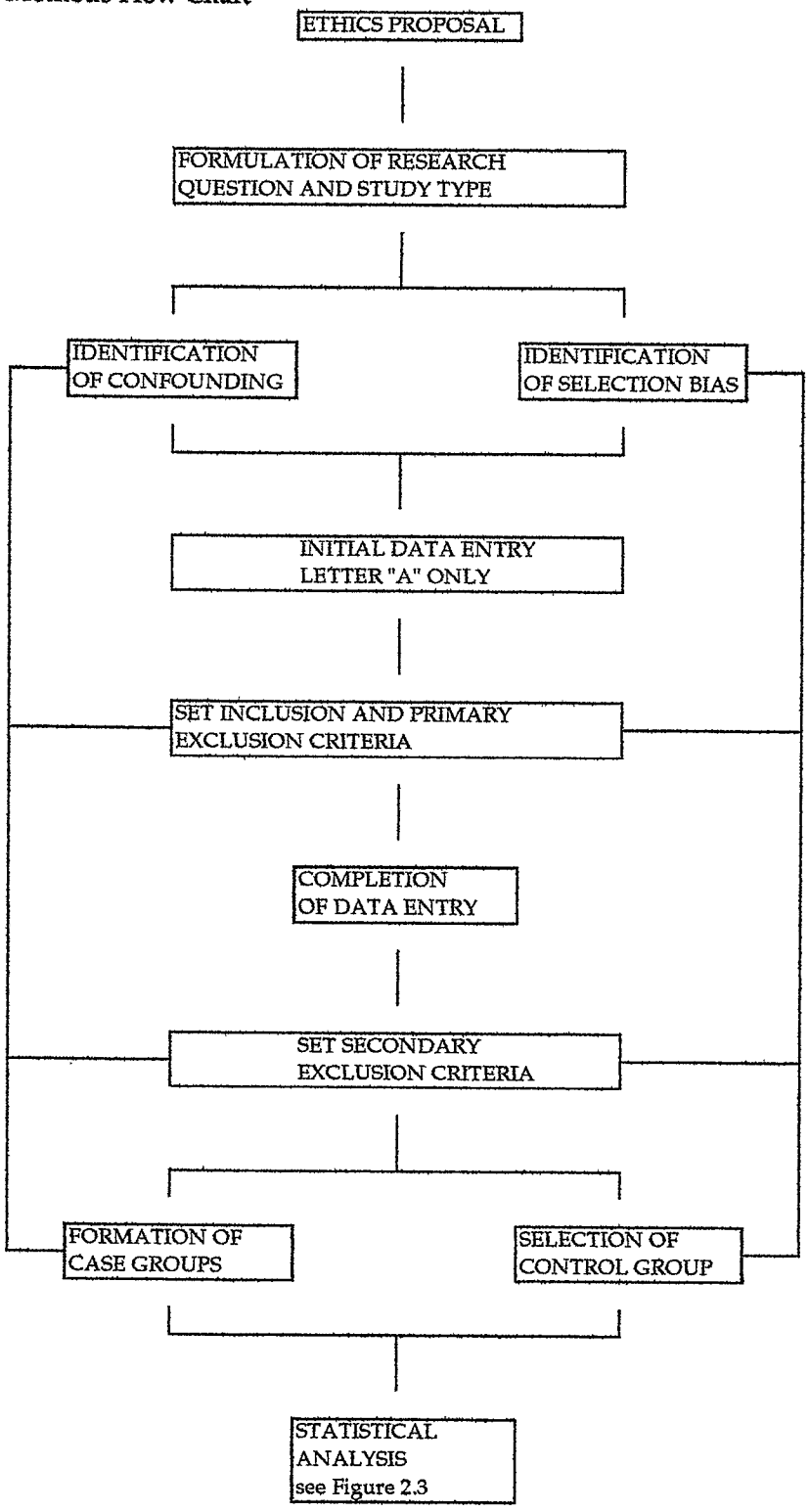
Precocious puberty is defined as the occurrence of puberty before the age of 8 years in girls and 9 years in boys *(Hardin & Pescovitz, cited in McAnarney et al, 1992)* and is diagnosed on the basis of clinical findings and laboratory results. The precocious development is isosexual when the development is common to the phenotypic sex of the individual and heterosexual when the development is characteristic of the opposite sex. "True precocious puberty" is due to premature maturation of the hypothalamic-pituitary axis *(Wyngaarden, & Smith, 1988)*, and hence will affect thyroid function.

CHAPTER 2

METHODS

The methodological stages of the study are outlined in Figure 2.1.

Figure 2.1 **Methods Flow Chart**



Ethics Proposal

Prior to commencing data entry, an application was made and approval granted from the School of Community Health, Faculty of Health Sciences Ethics Committee. This was a standard application as used by the University of Sydney ethics committee which is an NH&MRC (National Health and Medical Research Council) - based committee. This ethics proposal was also made to the Royal Alexandra Hospital for Children (RAHC) via Dr. John Coakley, Head of the Clinical Biochemistry Department. The application is contained in *Appendix A*. It was decided that provided that confidentiality of patient information was maintained throughout the study, there were no ethical problems in the use of these data.

Confidentiality was maintained by not removing at any time, the log book, or any data containing patient names from the Clinical Biochemistry Department of the RAHC; by having only one data entry person (myself) and these data being entered on site until completion. Once the data were entered and inclusion and primary exclusion criteria determined, patients' names were deleted from the computer files, prior to commencing statistical analyses.

Formulation of the Research Question and Study Type

The initial inspection of the raw data found that a number of different diagnoses and almost complete thyroid function test results for each entry were available. It was decided to investigate the relationship between the thyroid function test results for each patient (specifically thyroxine) and the diagnosis listed as little was known in this area at the time. This was done using the format of an epidemiological case-control study as the patients were identified first on disease status and then on exposure (thyroid function).

Hence the *study factors* for this study were the results of thyroid function tests for thyroxine (T_4), thyroid stimulating hormone (TSH) and triiodothyronine uptake, (T_3U) and the *outcome factors* were the various diagnostic groups investigated. Thus a *case-control study* consists of a case group (diagnostic group) and a control group (see *Selection of a Control Group*). The *research question* was thus the relationship between thyroid hormone levels and various diagnostic groups in children having thyroid function tests at the RAHC between 1980 and 1990.

Formation of Case Groups

A list of codes used for computer entry of diagnoses with corresponding and alternative meanings is contained in *Appendix B*. Preliminary statistical analyses were conducted in patients aged 3-18 years only, (n = 2998). Where more than one diagnosis was given, these were converted to a single diagnosis where possible. In the case where one diagnosis did not significantly interfere with the other, the combination was converted to the most significant diagnosis and then added to its respective diagnostic group. A list of these conversions for patients aged 3-18 years and less than 3 years is contained in *Appendix C*.

Diagnoses which were medically similar were then combined into single, larger diagnostic groups which varied in sample size (n = 2 to n = 465). A list of the diagnoses in these groups is contained in *Appendix D*, along with group reference numbers. Individual diagnoses which could not logically be added to a diagnostic group were not analysed and became part of the Miscellaneous group.

The main diagnosis of each diagnostic group was identified on the basis of its effect on the group when included and excluded in the calculation of a p-value (results not shown). If the diagnosis in question did not affect the p-value, it remained part of the original diagnostic group. If the diagnosis in question was responsible for an observed effect, either due to its relative sample size or significant p-value, it was

either analysed as a separate diagnostic group or used as the basis for the formation of a new diagnostic group, as indicated by similar reference numbers (Appendix D). All the decisions concerning the above conversions and combinations were done in consultation with Dr. John Coakley and Dr. John Earl at the RAHC.

Data Entry

Data entry was commenced in October 1993 and completed in February 1994. Data were entered onto *Microsoft Excel for Windows* version 4.0 at the RAHC. This spreadsheet was used instead of a standard database, due to the ease of entering and manipulating the data. Subsequent statistical analyses on these data were performed using *Excel* and *Spida* version 6.06, a DOS-based statistical package developed at Macquarie University, Sydney.

The raw data which were previously hand-recorded in a log book were arranged alphabetically and were thus computer-entered. Individual codes were used for each diagnosis as listed in Appendix B. Patient data were entered according to defined inclusion and exclusion criteria and subject to further exclusion at the completion of data entry (as detailed below). After all exclusions were made the total number of patients in the population for analysis was 4856 patients.

Confounding

It is especially important to consider the phenomenon of confounding in a case-control study as data on exposure are collected retrospectively. Confounding involves the possibility that "the observed association between two groups may be due in part or in total, to actual differences between the two groups under comparison", *(Hennekens & Buring, 1987)*. Thus the consideration of confounding is important in the interpretation of the findings of epidemiological studies, as confounding can often lead to an erroneous interpretation of the true association between exposure and disease and can even change the association of an observed effect *(Hennekens & Buring, 1987)*.

Potential confounders identified in this study were thyroid disease, other diseases which affect thyroid function, age, sex, puberty, year of diagnosis and some of the combined diagnoses. These were identified as potential confounders because they altered both the study factor (thyroid function) and outcome factor (diagnostic groups), (Figure 2.2). Standard methods used to control for confounding are randomization, matching, inclusion, exclusion and stratification. In this study *inclusion*, *exclusion*, and *stratification* were strategies used in dealing with confounding. (Figure 2.3). Primary and secondary exclusion criteria are presented in Tables 2.2 and 2.3.

Figure 2.2 Confounding

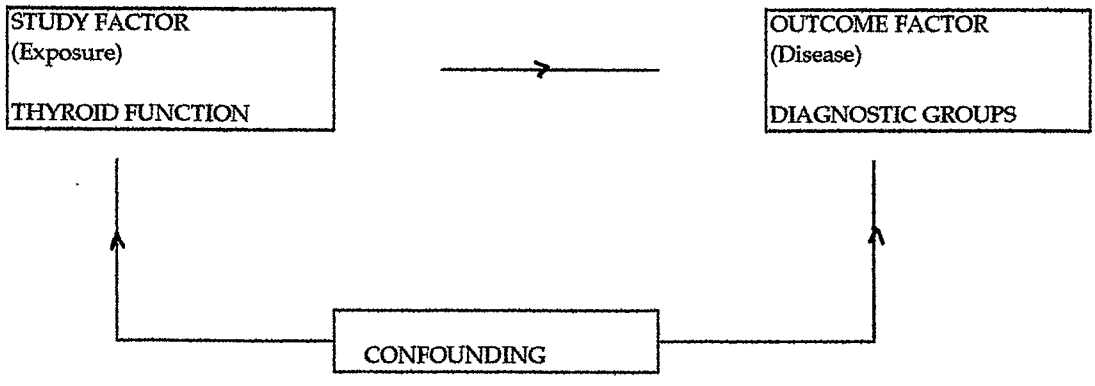
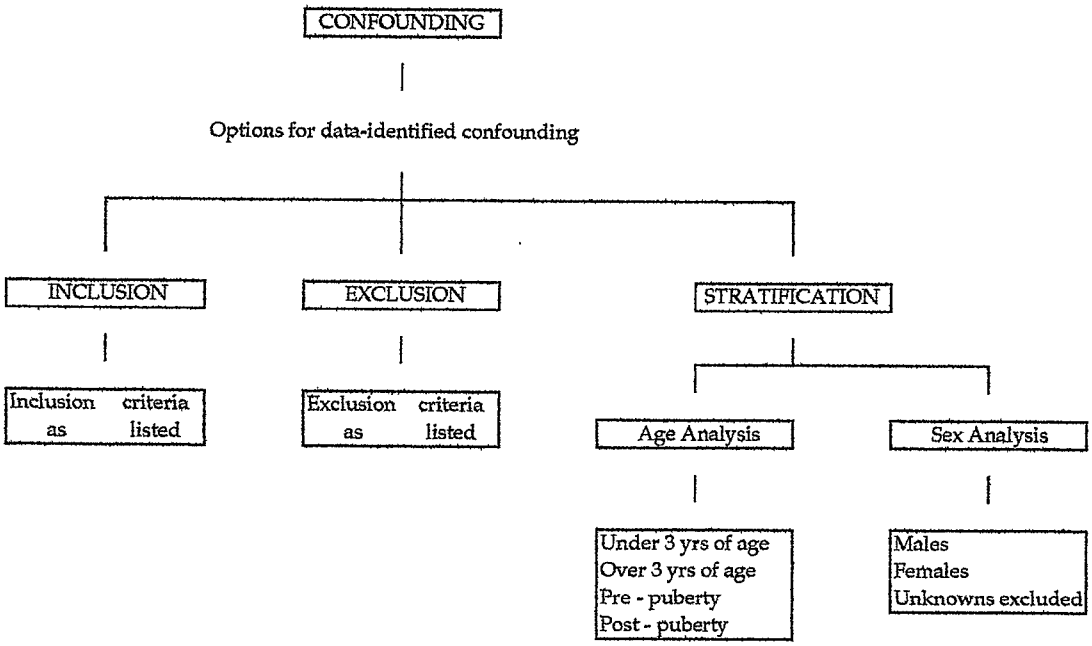


Figure 2.3 **Controlling for confounding**



Inclusion Criteria

Any patient aged up to and including 18 years of age attending the RAHC for thyroid function tests between 1980 and 1990 and recorded in the Clinical Biochemistry Department log book.

Age stratification

The data were divided into two age groups: (i) under 3 years of age and (ii) 3 years and over to 18 years of age. This division was necessary due to the changing normal range of T_4 levels in children by age. For children aged 3 years and over, there is a single normal range for T_4 and this is constant throughout this group (65-180 nmol/L). These ranges are not absolute and for ease of analysis children aged 3 years and over were analysed as a single group. For children aged less than 3 years of age, the ranges vary with age although there is a slight increase overall with age, (Table 2.1).

Table 2.1
Normal serum thyroxine ranges by age

Serum thyroxine (nmol/L)	Age
130 - 215	0 - 2 wks
100 - 215	2 - 4 wks
110 - 215	4 - 6 wks
95 - 190	6 - 8 wks
95 - 205	2 - 3 mths
85 - 180	3 - 4 mths
75 - 175	4 - 6 mths
75 - 180	6 - 9 mths
65 - 170	9 - 12 mths
75 - 160	1 - 2 yrs
90 - 155	2 - 3 yrs
65 -180	> 3 yrs

(RAHC, 1994)

For patients aged less than 3 years, the main diagnoses were examined graphically by plotting the number of cases per diagnosis versus age and the mean T_4 per diagnosis versus age. These results are presented in Chapter 5. It was decided that this would be the extent to which the data for patients aged less than 3 years of age would be examined due to the following:

a) the lack of a suitable control group in this population and,
b) the varying normal range for T_4 in this group.

These factors would make further analysis of this group difficult. Subsequent analyses were performed for patients aged 3 years and over.

Selection Bias

A case-control study, such as this, is one type of epidemiological investigation in which subjects are selected on whether the disease under investigation is absent (controls) or present (cases) in them. Selection bias needs careful consideration in case-control studies since the diseases have already occurred at the time of subject selection and data on exposure is gathered retrospectively. Selection bias can occur

whenever the inclusion of cases or controls into the study depends in some way on the exposure of interest *(Hennekens & Buring, 1987)*. In this study the *exposure* is thyroid function and the *disease* is the list of various diagnostic groups. In an attempt to control for selection bias in this study, patients with known thyroid disease were excluded.

Response Rate Estimation

In order to obtain information concerning selection of the data, a subset of the data were analysed for data on exclusions, i.e. response rate. Exclusions for the first letter of the alphabet ("A") were documented as follows. Table 2.2 lists the number of and type of entries excluded in each case from a total number of entries, (n = 447), prior to the rest of the data entry and exclusion. The numbers shown in brackets are for entries where "treatment" was listed as "no" (except for primary exclusions 4 and 5) and are mutually exclusive. The total number of primary exclusions for the letter "A" data entry equalled 221 (49.4%). These primary exclusion criteria were then used for subsequent data entry. Thus it is estimated that 50 per cent of the total data were excluded overall, primarily due to missing data.

At the completion of each letter of data entry, the data were sorted and duplicate entries deleted by comparing the name and age at the date of sample; leaving only the first chronological entry for the purposes of this analysis. Those entries of unknown sex were checked against later computerised laboratory results (where available) in the Department of Clinical Biochemistry at the RAHC, which included the sex of the patient. If a log book entry could be positively identified with a more recent computerised record by matching both the name and date of birth with the log book entry of the patient's age at the date the sample was taken, the patient's sex was changed from "unknown" to" male" or "female" respectively. If no match was made the patient's sex was left as "unknown". At the completion of all data entry secondary exclusions were made as detailed in Table 2.3.

Table 2.2 **Primary exclusion criteria***

1.	The patient was over 18 years of age *(2)*.
2.	No information on age was given *(5)*.
3.	The patient is the parent of a child also tested, regardless of age *(1)*.
4.	Treatment (usually T_4) was listed as "Yes" *(78)*.
5.	No information on treatment was given *(29)*.
6.	The patient was listed as being on any drug or treatment including lithium, growth hormone, chemotherapy and radiotherapy as these have potential interactive effects with the thyroid hormones *(32)*.
7.	The patient was participating in a trial, as treatment here was uncertain *(6)*.
8.	The patient had only a first initial or "Baby" listed as a first name as sex could not be determined from this information unless by diagnosis *(2)*.
9.	More than one surname was given *(1)*.
10.	No diagnosis was given *(6)*.
11.	Where the diagnosis was any of the following: a) Any known thyroid disease, e.g. hypothyroidism, goitre *(40)*. b) Any cancer except AML and ALL *(4)*. c) Any transplant patient, as these patients would most likely have been on drug therapy which may interact with the thyroid hormones *(1)*. d) "Post-disease" as only current disease was of interest in this study *(5)*.
12.	Follow-up to past disease or treatment *(7)*.

*Numbers in brackets are used to calculate the response rate for a subset of the data consisting of the letter "A"group, (n = 447). Total number of exclusions = 221.

Table 2.3 **Secondary exclusion criteria***

1.	Where no T_4 result was listed *(9)*.
2.	Thyroxin-binding globulin (TBG) deficiency. Upon checking for any apparent clinical reason for a low T_4 result, those with TBG < 12 mg/L were eliminated, where listed *(10)*.
3.	Familial TBG excess (TBG > 28 mg/L), where listed *(2)*.
4.	TBG malfunction, indicated by a T_3U result of < 0.8 nmol/L and > 1.2 nmol/L, where listed *(139)*.
5.	Nephrotic Syndrome, as this has been linked to a loss of protein *(6)*.
6.	Primary hypothyroidism indicated by a TSH level > 7.0 mU/L, where listed. Therefore Short Stature due to primary hypothyroidism was also eliminated *(166 of 3782 with TSH value listed)*.
7.	Pituitary Axis Disease, as this may be linked to secondary hypothyroidism *(1)*.
8.	Hypothalamic Disorder/Disturbance, as this may be linked to secondary hypothyroidism *(3)*.
9.	Where no definite diagnosis was listed or where the requesting physician was uncertain of the diagnosis (where not excluded previously). These cases would be unable to be placed in one diagnostic group for investigation and their inclusion would lead to error in the final result *(95)*.
10.	Any neurological disorders remaining after previous eliminations as these patients may be on treatment which may affect thyroid function tests. A list of these disorders is contained in *Appendix E (160)*.

*Numbers in brackets are used to calculate the response rate for the total study population, (n = 4856).

Selection of a control group

In a case-control study, it is often appropriate to choose a group representative of the general population. As this control group is compared to other diagnostic groups, a control group as similar to these groups as possible, but without the diseases themselves, is required. In an attempt to identify an appropriate control group for the various diagnostic groups selected, an overall review of the data was conducted. Medically opposite diagnostic groups were identified in the data and compared against one another for T_4, T_3U and TSH by age and puberty (Tables 2.4 to 2.6). Generally, the groups are not significantly different from one another, indicating the original study population was fairly homogeneous. Although there are significant results for T_3U, the small sample sizes in the T_3U data need to be considered here.

The Short Stature diagnostic group was seen as a possible control group. Short Stature due to primary hypothyroidism was eliminated, so the remaining patients were most likely just genetically short, which is unrelated to thyroid function. This group was also not significantly different from the Tall Stature group. It had a large sample size and this would serve to increase the power of the analysis when comparing case groups to the Short Stature diagnostic group, as the probability of a more accurate result is increased with a larger sample size.

Table 2.4a **T4: Opposite diagnostic groups by sex**

Ref	Group	No. per group			Mean T4 (nmol/L)			p - value		
		M	F	Total	M	F	Total	M	F	Total
1	SHORT STATURE	781	374	1155	120.6	126.8	122.6	-	-	-
5A	TALL STATURE	19	44	63	129.3	118.5	121.8	0.104	0.023	0.715
3B	WEIGHT GAIN	3	5	8	105.3	123.6	116.8	-	-	-
4C	WEIGHT LOSS	13	18	31	128.8	111.2	118.6	0.090	0.213	0.839
7A	PRECOCIOUS PUBERTY	13	46	59	125.2	126.7	126.4	-	-	-
7B	PUBERTAL DELAY	29	10	39	116.8	119.7	117.6	0.195	0.435	0.096
12A	MENSTRUAL PROBLEMS	0	17	17	-	117.6	117.6	-	-	-
12B	AMENORRHOEA	0	17	17	-	116.7	116.7	-	0.757	0.757
17A	ALOPECIA	8	13	21	128.6	120.1	123.3	-	-	-
17B	HIRSUTISM	0	12	12	-	118.5	118.5	-	0.821	0.492

Table 2.4b **T4: Opposite diagnostic groups by puberty**

Ref	Group	No. per group			Mean T4 (nmol/L)			p - value		
		3-11 yrs	>11-18 yrs	Total	3-11 yrs	>11-18 yrs	Total	3-11 yrs	>11-18 yrs	Total
1	SHORT STATURE	662	493	1155	124.6	120.0	122.6	-	-	-
5A	TALL STATURE	38	25	63	127.2	113.5	121.8	0.519	0.125	0.715
3B	WEIGHT GAIN	0	8	8	-	116.8	116.8	-	-	-
4C	WEIGHT LOSS	11	20	31	135.6	109.2	118.6	-	0.423	0.839
7A	PRECOCIOUS PUBERTY	55	4	59	127.7	108.5	126.4	-	-	-
7B	PUBERTAL DELAY	0	39	39	-	117.6	117.6	-	0.675	0.096
12A	MENSTRUAL PROBLEMS	4	13	17	115.0	119.2	117.6	-	-	-
12B	AMENORRHOEA	0	17	17	-	116.7	116.7	-	0.673	0.757
17A	ALOPECIA	17	4	21	126.8	108.8	123.3	-	-	-
17B	HIRSUTISM	1	11	12	134.0	117.1	118.5	0.671	0.377	0.492

Table 2.5a **TSH: Opposite diagnostic groups by sex**

Ref	Group	No. per group			Mean TSH (nmol/L)			p - value		
		M	F	Total	M	F	Total	M	F	Total
1	SHORT STATURE	762	355	1117	2.76	2.73	2.75	-	-	-
5A	TALL STATURE	14	35	49	2.94	2.50	2.63	0.591	0.459	0.596
3B	WEIGHT GAIN	2	3	5	0.85	3.27	2.30	-	-	-
4C	WEIGHT LOSS	5	10	15	2.34	1.69	1.91	0.281	0.187	0.864
7A	PRECOCIOUS PUBERTY	13	36	49	3.01	2.19	2.41	-	-	-
7B	PUBERTAL DELAY	24	10	34	2.53	2.77	2.60	0.547	0.156	0.343
12A	MENSTRUAL PROBLEMS	0	12	12	-	1.73	1.73	-	-	-
12B	AMENORRHOEA	0	14	14	-	2.56	2.56	-	0.214	0.214
17A	ALOPECIA	2	7	9	3.70	2.63	2.87	-	-	-
17B	HIRSUTISM	0	7	7	-	1.89	1.89	-	0.416	0.235

Table 2.5b **TSH: Opposite diagnostic groups by puberty**

Ref	Group	No. per group			Mean TSH (nmol/L)			p - value		
		3-11 yrs	>11-18 yrs	Total	3-11 yrs	>11-18 yrs	Total	3-11 yrs	>11-18 yrs	Total
1	SHORT STATURE	635	482	1117	2.83	2.66	2.75	-	-	-
5A	TALL STATURE	31	18	49	2.88	2.19	2.63	0.720	0.140	0.596
3B	WEIGHT GAIN	0	5	5	-	2.30	2.30	-	-	-
4C	WEIGHT LOSS	5	10	15	2.36	1.68	1.91	-	0.756	0.864
7A	PRECOCIOUS PUBERTY	46	3	49	2.36	3.07	2.41	-	-	-
7B	PUBERTAL DELAY	0	34	34	-	2.60	2.60	-	0.485	0.343
12A	MENSTRUAL PROBLEMS	4	8	12	1.38	1.91	1.73	-	-	-
12B	AMENORRHOEA	0	14	14	-	2.56	2.56	-	0.500	0.214
17A	ALOPECIA	7	2	9	2.94	2.60	2.87	-	-	-
17B	HIRSUTISM	1	6	7	5.50	1.28	1.89	0.681	1.000	0.235

Table 2.6a **T3U: Opposite diagnostic groups by sex**

Ref	Group	No. per group			Mean T3U			p - value		
		M	F	Total	M	F	Total	M	F	Total
1	SHORT STATURE	781	374	1155	0.97	0.96	0.97	-	-	-
5A	TALL STATURE	19	44	63	0.94	0.95	0.95	0.064	0.268	0.034
3B	WEIGHT GAIN	3	5	8	0.94	0.90	0.92	-	-	-
4C	WEIGHT LOSS	13	18	31	0.97	0.98	0.98	0.164	0.030	0.008
7A	PRECOCIOUS PUBERTY	13	46	59	0.96	0.95	0.95	-	-	-
7B	PUBERTAL DELAY	29	10	39	0.98	0.94	0.97	0.293	0.803	0.191
12A	MENSTRUAL PROBLEMS	0	17	17	-	8.35	8.35	-	-	-
12B	AMENORRHOEA	0	17	17	-	0.96	0.96	-	0.209	0.209
17A	ALOPECIA	8	13	21	0.97	0.97	0.97	-	-	-
17B	HIRSUTISM	0	12	12	-	0.96	0.96	-	0.952	0.877

Table 2.6b **T3U: Opposite diagnostic groups by puberty**

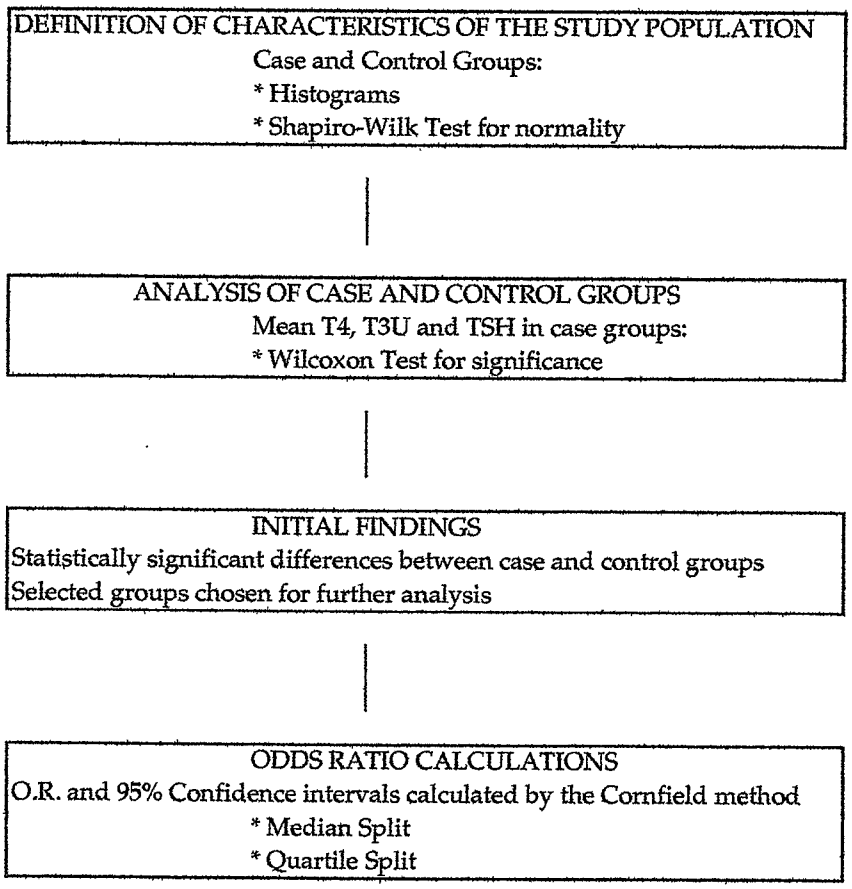
Ref	Group	No. per group			Mean T3U			p - value		
		3-11 yrs	>11-18 yrs	Total	3-11 yrs	>11-18 yrs	Total	3-11 yrs	>11-18 yrs	Total
1	SHORT STATURE	662	493	1155	0.96	0.97	0.97	-	-	-
5A	TALL STATURE	38	25	63	0.93	0.98	0.95	0.001	0.356	0.034
3B	WEIGHT GAIN	0	8	8	-	0.92	0.92	-	-	-
4C	WEIGHT LOSS	11	20	31	1.0	0.98	0.98	-	0.020	0.008
7A	PRECOCIOUS PUBERTY	55	4	59	1.0	0.95	0.95	-	-	-
7B	PUBERTAL DELAY	0	39	39	-	0.97	0.97	-	0.297	0.191
12A	MENSTRUAL PROBLEMS	4	13	17	1.03	0.98	8.35	-	-	-
12B	AMENORRHOEA	0	17	17	-	0.96	0.96	-	0.331	0.209
17A	ALOPECIA	17	4	21	0.97	0.97	0.97	-	-	-
17B	HIRSUTISM	1	11	12	0.90	0.97	0.96	0.339	0.947	0.877

Analysis

Statistical Analysis

The steps taken in the investigation of the study and outcome factors are shown in Figure 2.4.

Figure 2.4 **Investigation of study and outcome factors**



As T_4 levels were the main exposure or study factor investigated, the data were initially inspected to see if they were normally distributed by plotting data distribution by study factor (thyroid function) and outcome factor (diagnostic group) and then these factors were stratified by age, sex, puberty and year of diagnosis. Histograms were initially used to inspect the groups which varied in distribution between normally and non-normally distributed data.

Five of the thirteen groups were not normally distributed. This was confirmed by applying the Shapiro-Wilk Test for normality. A value of less than 0.95 here indicates the data was not normally distributed (Table 2.7). Figures 2.5 and 2.6 give examples of histograms for two groups from the entire population (Diabetes and Developmental Delay) which exhibit normal and non-normal distribution respectively.

Figure 2.5 **Total population: Diabetes histogram**

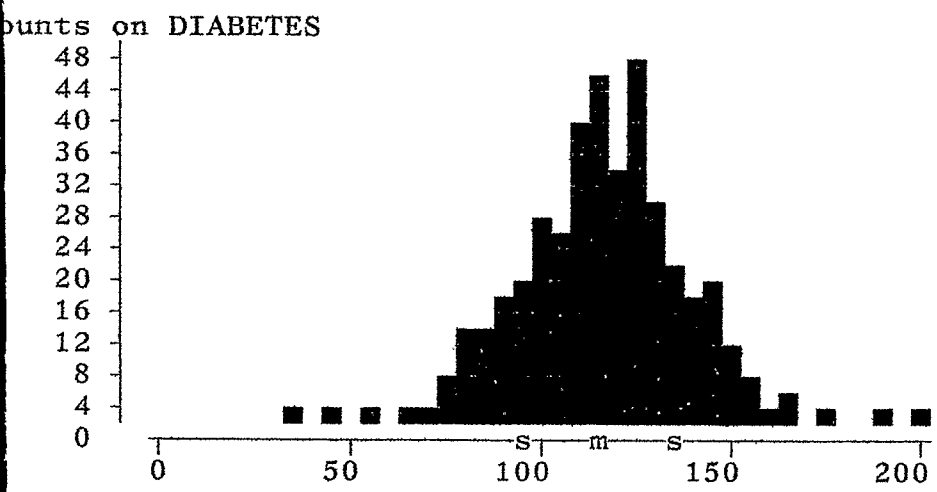
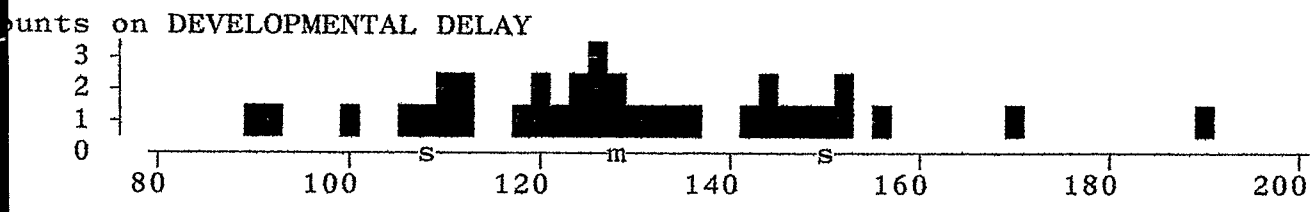


Figure 2.6 **Total population: Developmental Delay histogram**



In order to see if there was a relationship between study and outcome factors, the mean T_4, TSH and T_3U were compared for each diagnostic group to the control group (Short Stature). As the diagnostic groups varied in distribution, the Wilcoxon Rank Sum Test was used for significance testing of the data to produce a p-value. Where a statistically significant mean difference ($p < 0.05$) between case groups and the control group were found for T_4, a further analysis was performed in order to produce an odds ratio. This value represents the risk of a particular diagnostic group having a higher or lower T_4 value compared to the control group.

Diagnoses found to have a significantly different T_4 from the control group were then reported and stratified into low T_4 and high T_4 categories with a subsequent analysis on TSH and T_3U. Due to the nature of the age and sex confounding described previously, the diagnostic groups in these categories were also stratified by sex and then re-stratified into pre- and post-puberty groups and analysed. In the case where only one-sided stratification was possible, i.e. stratification into males or females only, or into 3-11 years or >11-18 years groups only, due to either small sample size or nature of the disease, these groups were compared against the corresponding sub-group in the control (Short Stature).

Table 2.7 **Shapiro-Wilk test for normality**

Ref	Group	T4	TSH	T3U
1	SHORT STATURE (control)	0.987	0.938	0.979
	Significantly low T4			
2B	SELECTED DIABETES	0.991	0.878	0.982
10A	THALASSAEMIA	0.984	0.972	0.961
13A	GROWTH HORMONE DEFICIENCY	0.946	0.945	0.930
4D	ANOREXIA NERVOSA	0.970	0.943	0.944
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	0.980	0.958	0.862
11D	ALL PSYCHOLOGICAL DISORDERS	0.970	0.817	0.902
4B	CYSTIC FIBROSIS	0.948	0.948	0.983
	Significantly high T4			
3A	OBESITY	0.976	0.944	0.970
18	DEAFNESS	0.887	0.962	0.987
4A	FAILURE TO THRIVE	0.979	0.971	0.961
20B	SLIPPED EPIPHYSES	0.936	0.930	0.934
14A	TURNER'S SYNDROME	0.982	0.953	0.929
9A	JUVENILE CHRONIC ARTHRITIS	0.921	0.960	0.899

Odds Ratio

Odds ratios at the 95% confidence level were calculated for patients aged 3 years and over, using the Cornfield method. *Epi Info* version 5.01 was used to perform this analysis. Odds ratios were calculated for sex and age stratified data in the above groups on T_4 levels only, in order to assess the risk of a low or high T_4 respectively for each diagnosis.

Both median and quartile splits were calculated from the control group. The control group data was divided into half by the median for Short Stature (123 nmol/L) and again into quartiles by the interquartile split and the number of values in each of these splits noted. The number of values in each half or quartile respectively for each diagnostic group were then compared against the number of values in each of these splits for the control group.

For example, from the Selected Diabetes diagnostic group a 2 x 2 table can be constructed with the following data in order to calculate a median split on this group (Figure 2.7):

Figure 2.7
Median odds ratio calculation for the Selected Diabetes diagnostic group (case group) **against Short Stature** (control group).

Cell	Number per cell
a	The number of case values below the control median = 279
b	The number of control values below the control median = 611
c	The number of case values above the control median = 183
d	The number of control values above the control median = 544

Odds Ratio calculation

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc} = \frac{279 \times 544}{611 \times 183} = \frac{151776}{111813} = 1.357 = \mathbf{1.4}$$

Stratification

The Obesity and Failure to Thrive pre- and post-pubertal groups were further sub-stratified by sex in order to attempt to explain the earlier findings. This was possible since the total number of patients in these sub-groups was sufficiently large enough to allow for further statistical testing. However, only T_4 and TSH groups were tested here since data for T_3U sub-stratification were insufficient to allow for further testing.

CHAPTER 3

GENERAL RESULTS

The data presented in the results section were analysed as per the general statistical analysis protocol presented in Chapter 2. Initially, the characteristics of the general population are presented for both case and control groups. Histograms of the total study population and the control group were prepared using *Excel*. Each potential confounder was investigated separately and is described below.

In this general overview, potential confounders of age, sex, puberty and year of diagnosis are analysed to see if they are confounders in this data set, i.e. do they affect both the diagnostic state and thyroid function. An *a priori* assumption based on clinical knowledge was made that different diagnostic states will be affected by age and sex. Hence a *post hoc* data analysis on age and sex for each diagnostic group is not presented here but an indication is represented by the number of patients plotted by the confounding variable.

Characteristics of the Study Population

Age

Overall age group representations are shown in Table 3.1 and Figures 3.1a and 3.1b. The study population was split on age (< 3 years of age and 3-18 years of age), as age is an *interaction factor* in this study. Interaction can be thought of as when two components of a disease share a causal responsibility for that disease *(Rothman, 1986)*. In this case, the varying normal T_4 ranges in patients aged less than 3 years of age compared to those aged 3 years and over, indicate that the two groups are metabolically different and hence not a homogeneous population.

It was decided to restrict the main analysis to patients aged 3 years and over, the results of which are presented in Chapter 4. The results for patients aged less than 3 years are presented separately in Chapter 5.

Figure 3.1a shows the number of patients tested by age group and Figure 3.1b the mean T_4 for each of these groups. All the T_4 results listed are for total T_4. Thyroid testing of children is most commonly requested for neonates and during puberty and this is reflected here with the highest number of tests in these groups. There is a general decrease in mean T_4 with age as was expected.

Table 3.1
Total study population by age

Age (yrs)	Number of patients	Mean T4 (nmol/L)
<= 1	621	153.9
>1 - 2	257	134.9
>2 -3	193	134.7
>3 - 4	164	132.4
>4 - 5	182	129.4
>5 - 6	145	129.1
>6 - 7	183	125.2
>7 - 8	179	127.2
>8 - 9	200	125.1
>9 -10	182	125.2
>11 - 12	292	123.2
>12 - 13	272	118.4
>13 - 14	283	117.1
>14 - 15	243	115.6
>15 - 16	188	114.3
>16 - 17	122	111.8
>17 - 18	53	114.8

Figure 3.1a
Total study population: Number of patients by age

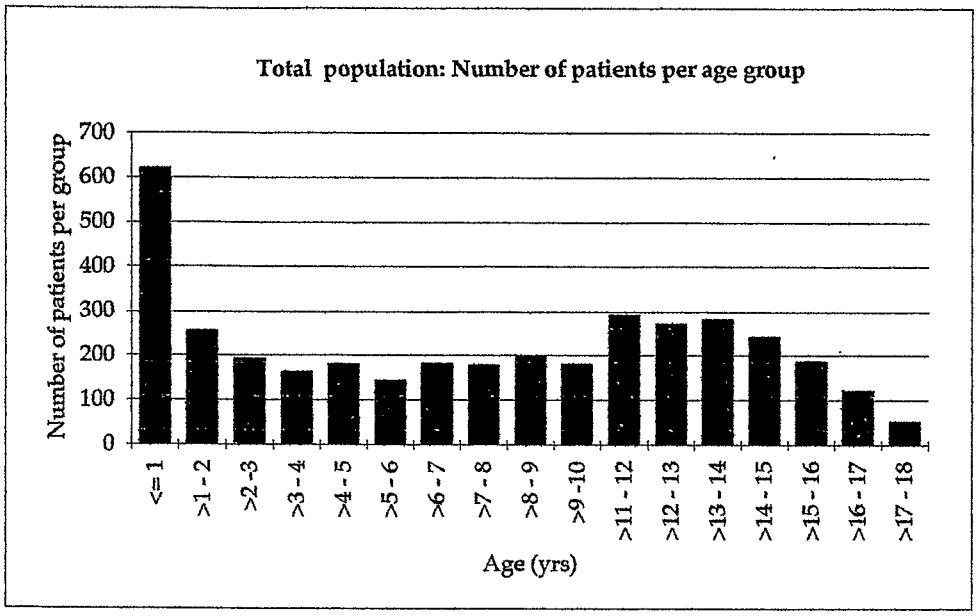
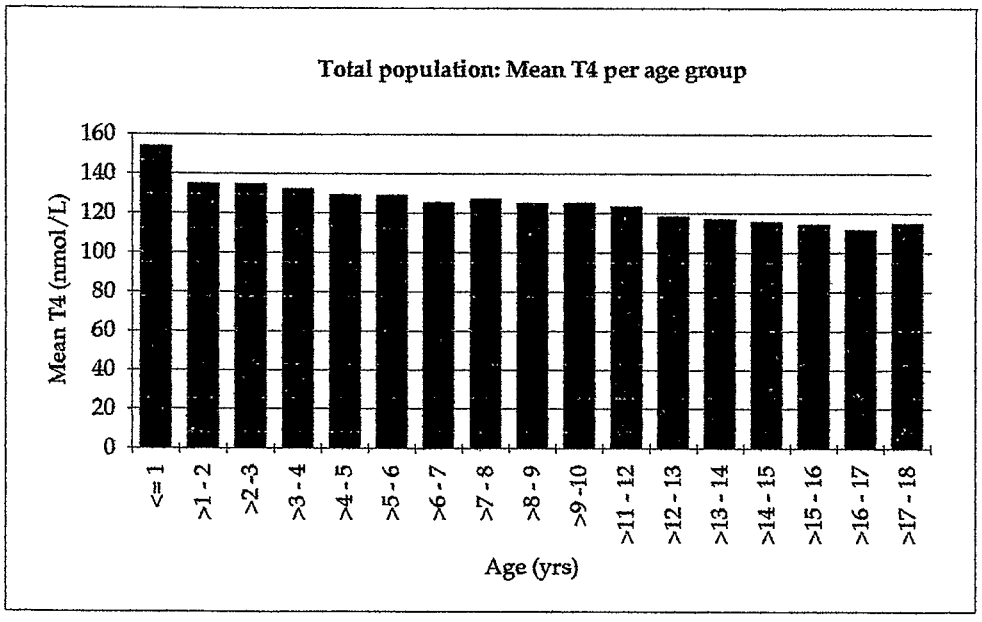


Figure 3.1b
Total study population: Mean T4 per age group



Puberty and Sex

Data for puberty and sex are presented in Table 3.2. Differences occurred in the data overall by sex and puberty. Differences also occurred upon stratification between pre- and post-puberty groups and between males and females.

Figure 3.2a shows the number of patients, and Figure 3.2b the Mean T_4 in the pre- and post-puberty groups for both males and females and overall by sex. Figure 3.2b shows a possible link between T_4 levels and puberty, especially pre- and post-puberty, with a decrease in T_4 levels post-puberty for both males and females. It also indicates a possible link between T_4 levels and sex, with females having a slightly higher T_4 than males in this population.

Table 3.2
Sex and puberty variations in T4

Sex/Age (yrs)	Number per group	Mean T4 (nmol/L)
Males: 3 - 11	779	124.82
Males: >11 -18	775	116.45
All males	2105	127.30
Females: 3 - 11	754	129.22
Females: >11 -18	678	118.58
All females	1912	129.91

Figure 3.2a
Pre- and post-puberty: Number of patients per age group, by sex

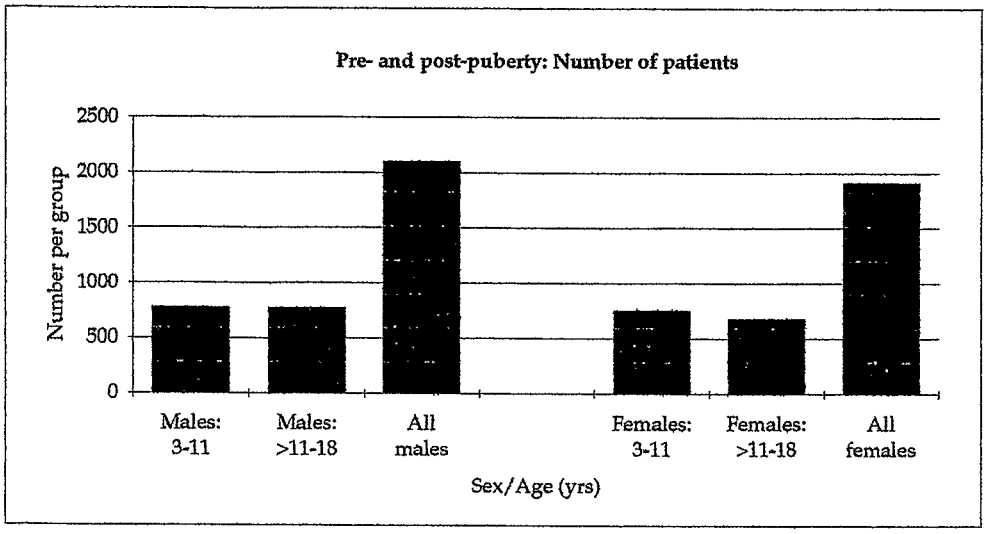
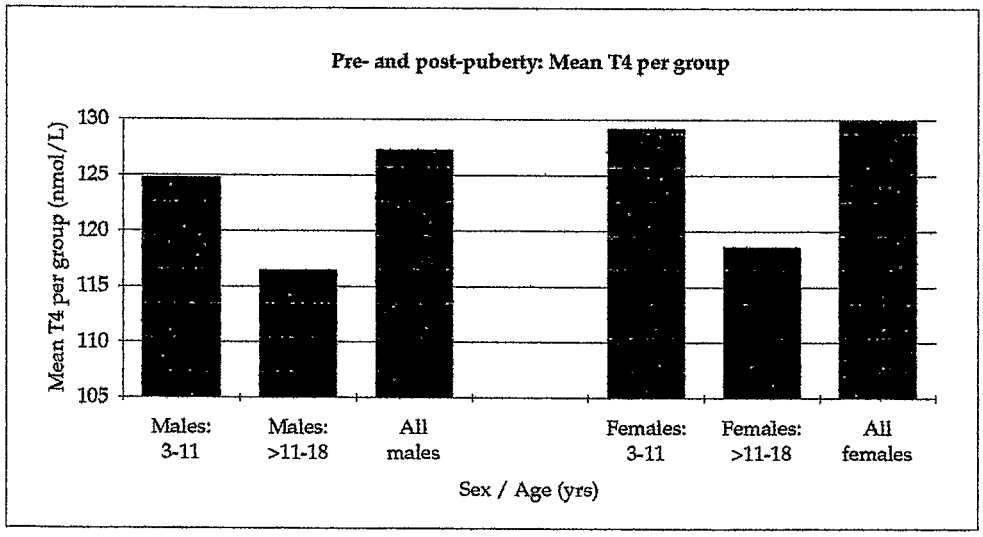


Figure 3.2b
Pre- and post-puberty: Mean T4 per age group, by sex



Year of Diagnosis

The number of patients and the mean T_4 per year of diagnosis for the total study population and the control group are presented in Table 3.3 and Table 3.4 respectively.

Figure 3.3a shows an overall increase in the number of patients tested per year between 1980 and 1990 in the total study population, as is expected. During 1980-1985 the number of patients tested is fairly consistent from year to year with a slight decrease in 1982. There appears to be a more consistent rise in the number of patients tested during 1986-1990. Figure 3.3b shows the mean T_4 for the total population of patients tested during 1980-1990. It is known that the assay method did not change over this period, but there was a change of operator performing the assay. This is discussed further in Chapter 6.

Table 3.3
Total study population:
Number of patients and Mean T4
per year of diagnosis

Year of Diagnosis	Number of patients	Mean T4 (nmol/L)
1980	326	124.6
1981	326	124.8
1982	267	124.3
1983	328	122.5
1984	321	121.0
1985	292	123.5
1986	349	125.7
1987	385	132.2
1988	416	132.6
1989	476	131.5
1990	531	139.8

Figure 3.3a
Total study population: Number of patients per year of diagnosis

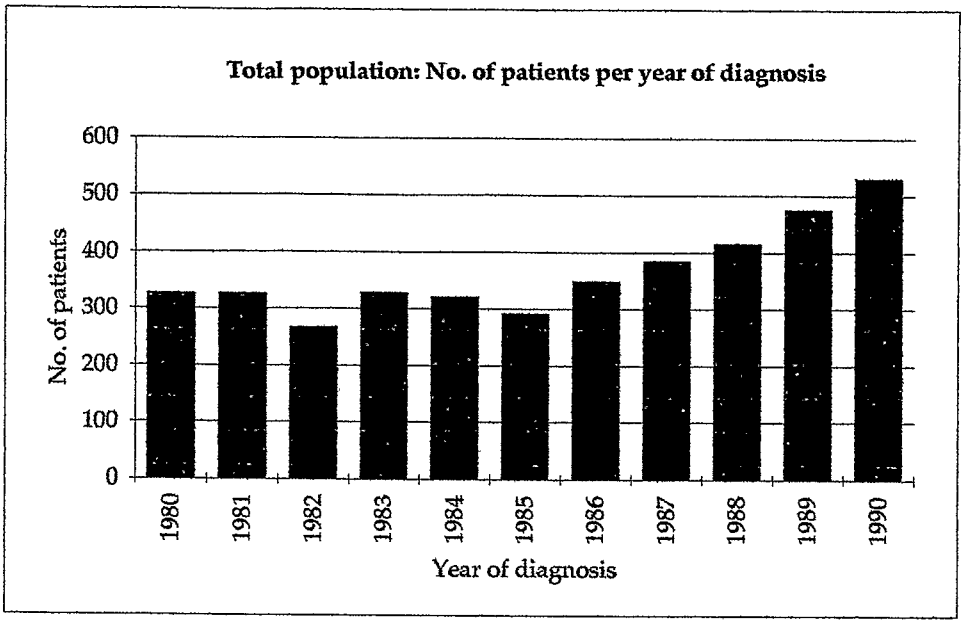
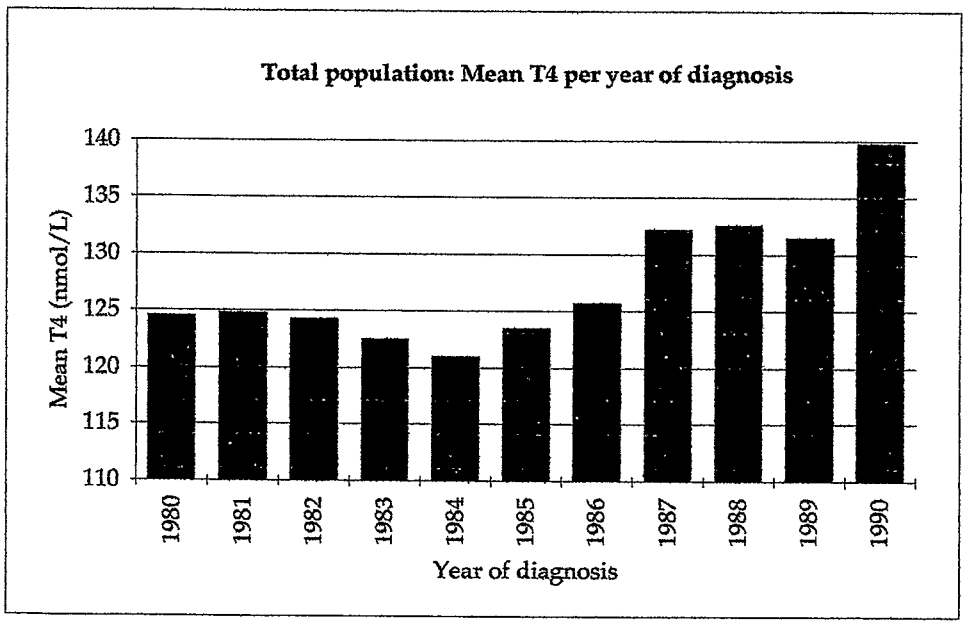


Figure 3.3b
Total study population: Mean T4 per year of diagnosis



As the control group showed similar trends in both the number of patients tested per year (Figure 3.4a) and the mean T_4 per year of diagnosis (Figure 3.4b), it was concluded that this would probably not influence the analysis and interpretation of the results. A further analysis could compare only patients aged 3-18 years with the control group, as this would give a better indication of the trends over time in this age group.

Table 3.4
Short stature (control) group: Number of patients and Mean T4 per year of diagnosis

Year of Diagnosis	Number of patients	Mean T4 (nmol/L)
1980	95	115.9
1981	119	117.2
1982	106	117.1
1983	117	120.8
1984	93	121.3
1985	85	118.3
1986	86	119.8
1987	109	128.5
1988	130	126.3
1989	105	122.8
1990	110	137.8

Figure 3.4a
Short stature (control) group: Number of patients per year of diagnosis

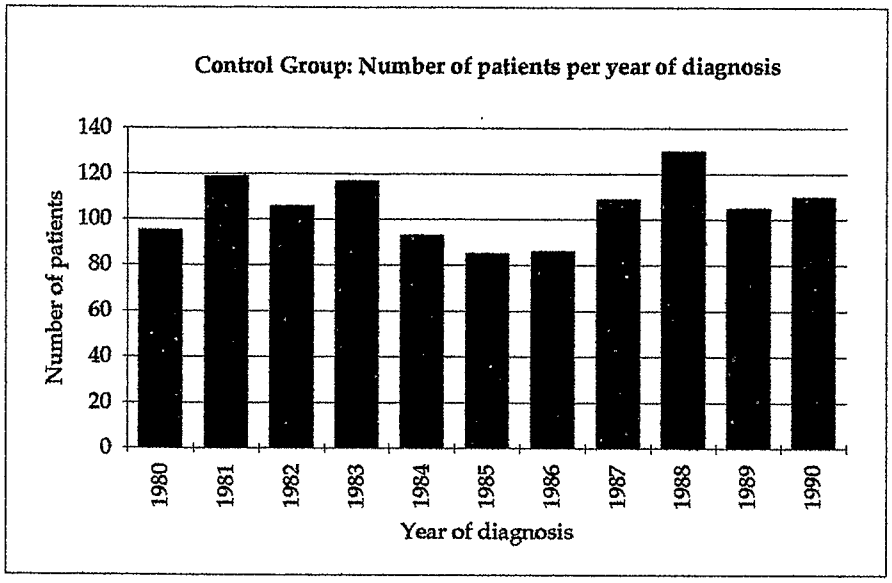
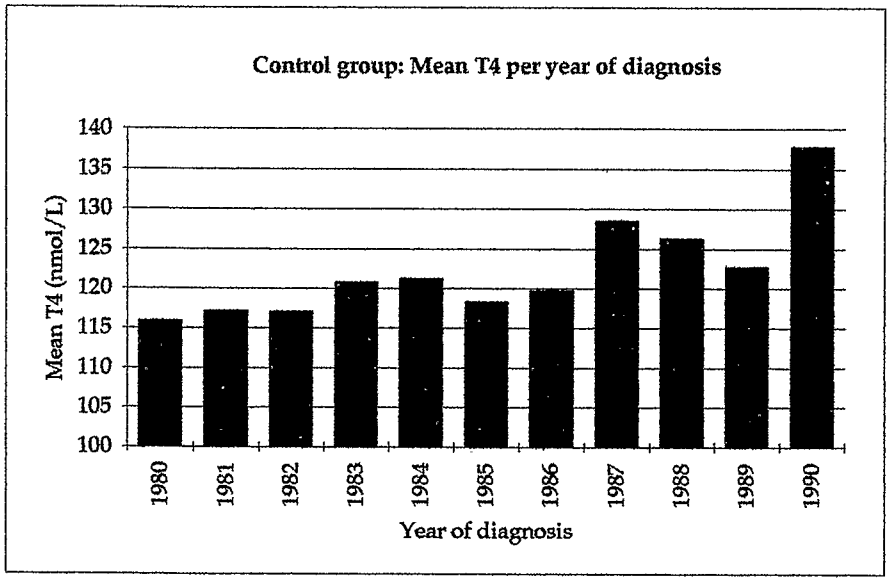


Figure 3.4b
Short stature (control) group: Mean T4 per year of diagnosis



Disease frequency

A breakdown of the frequency of diagnoses encountered in the total population are tabulated separately for patients aged less than 3 years of age (*Appendix F*) and for patients aged 3-18 years (*Appendix G*). This is the frequency of each diagnosis as it occurred after all exclusions and combinations described previously were made.

CHAPTER 4

RESULTS

Characteristics of the control group

A summary of the characteristics of the control group by confounding factors is presented in Table 4.1. All the T_4 results listed are for total T_4. The overall mean T_4 of the control group was 122.6 nmol/L which falls close to the median of the normal range for T_4 (65-180 nmol/L). The mean T_4 values for males and females, and pre- and post- puberty groups also approached the median. It is interesting to note that the control group (Short Stature) had the highest number of patients of any other diagnostic group (n = 1155) and this subsequently helped to increase the power of the analysis.

Table 4.1 **Characteristics of the control group - Short Stature**

Thyroid function test	Number of of patients	% total	Mean	Standard Deviation
T4				
M	781	67.6%	120.6	20.50
F	374	32.4%	126.8	22.13
3-11 yrs	662	57.3%	124.6	21.26
>11-18 yrs	493	42.7%	120.0	20.96
Group total	1155	100%	122.6	21.23
TSH				
M	762	68.2%	2.76	1.47
F	355	31.8%	2.73	1.52
3-11 yrs	635	56.8%	2.83	1.52
>11-18 yrs	482	43.2%	2.66	1.43
Group total	1117	100%	2.75	1.49
T3U				
M	781	67.6%	0.97	0.07
F	374	32.4%	0.96	0.06
3-11 yrs	662	57.3%	1.01	0.07
>11-18 yrs	493	42.7%	1.01	0.07
Group total	1155	100%	1.01	0.07

As previously indicated in Chapter 3, sex and puberty are confounders and thus the data are individually analysed, stratifying the data for male, female, 3-11 years and 11-18 years groups respectively.

Distribution of thyroxine levels by cases and control

Seventy-eight separate diagnostic groups were identified in patients aged 3-18 years. Twenty-one diagnostic groups showed a statistically significant mean difference for T_4, ($p < 0.05$), using the Wilcoxon Rank Sum Test for non-normally distributed data, (Table 4.2). Those that did not show a statistically significant mean difference for T_4 compared to the control group are listed in Table 4.3.

Table 4.2 **Initial T4 analysis by diagnostic group: Significant results**

Ref.	Diagnostic Group	Number per group	Mean T4 (nmol/L)	p - value
1	SHORT STATURE GROUP (control)	1155	122.6	-
2A	ALL DIABETES	465	116.5	0
2B	SELECTED DIABETES	462	116.4	0
3A	OBESITY	174	128.8	0
18	DEAFNESS	25	137.8	0.000
10A	THALASSAEMIA	52	113.1	0.001
4A	FAILURE TO THRIVE	46	134.0	0.001
13A	GROWTH HORMONE DEFICIENCY	50	114.0	0.002
11A	ANXIETY	4	94.0	0.002
27	MISCELLANEOUS GROUP	217	127.6	0.003
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	20	106.7	0.003
4D	ANOREXIA NERVOSA	17	104.5	0.003
13C	ALL ENDOCRINE DISORDERS (non-thyroidal)	81	116.0	0.004
9D	JUVENILE CHRONIC ARTHRITIS + ARTHRITIS	13	142.2	0.007
20B	SLIPPED EPIPHYSES	9	138.3	0.009
14A	TURNER'S SYNDROME	47	129.8	0.011
9B	CONNECTIVE TISSUE DISEASE	20	136.3	0.011
9A	JUVENILE CHRONIC ARTHRITIS	8	145.9	0.012
4G	SHORT BOWEL SYNDROME	2	163.5	0.013
11D	ALL PSYCHOLOGICAL DISORDERS	18	110.9	0.020
11B	BEHAVIOUR DISORDER	3	96.0	0.025
4B	CYSTIC FIBROSIS	32	112.6	0.037

N.B. Groups in bold selected for further analysis

Table 4.3 **Initial T4 analysis by diagnostic group: Non-significant results**

Ref.	Diagnostic Group	Number per group	Mean T4 (nmol/L)	p - value
8	DEVELOPMENTAL DELAY	47	129.2	0.061
21B	HYPOGONADISM	6	135.0	0.090
10C	SELECTED BLOOD DISORDERS	12	132.6	0.137
20A	DELAYED BONE AGE	6	136.3	0.144
19B	ABDOMINAL PAIN	9	129.4	0.159
21A	GYNAECOMASTIA	10	114.0	0.170
19E	CONSTIPATION + ABDOMINAL PAIN + DIARRHOEA	20	127.0	0.189
9E	SELECTED CONNECTIVE TISSUE DISEASE	12	129.9	0.193
7B	PUBERTAL DELAY	39	117.6	0.216
7A	PRECOCIOUS PUBERTY	59	126.4	0.223
23	RENAL DISORDERS	16	130.4	0.236
9C	ARTHRITIS	5	136.2	0.238
14E	CYSTINOSIS	6	138.3	0.242
4I	MALABSORPTION	2	109.0	0.247
19C	CONSTIPATION + ABDOMINAL PAIN	19	126.4	0.253
14D	PRADER-WILLI SYNDROME	8	113.9	0.256
12B	ALL AMENORRHOEA	17	116.7	0.257
15B	ACUTE MYELOBLASTIC LEUKAEMIA	5	132.0	0.261
4J	POOR/SLOW WEIGHT GAIN	2	107.5	0.264
4K	MALNUTRITION	1	142.0	0.290
25A	SYNCOPE	6	128.8	0.324
14B	DOWN'S SYNDROME	30	118.2	0.362
16C	MALAISE	3	112.7	0.367
22B	SWEATING	7	129.6	0.385
14F	KLINEFELTER'S SYNDROME	1	139.0	0.404
12A	SELECTED MENSTRUAL DISORDERS	17	117.6	0.413
16B	WEAKNESS	5	116.0	0.421
4C	WEIGHT LOSS	31	118.6	0.432
24C	NAUSEA + VOMITING	8	129.3	0.445
25D	HEADACHES	6	119.2	0.463
19D	DIARRHOEA	1	137.0	0.464
17B	HIRSUTISM	12	118.5	0.484
13D	SELECTED ENDOCRINE DISORDERS (non-thyroidal)	31	119.3	0.504
3B	WEIGHT GAIN	8	116.8	0.520
5B	ALL TALL STATURE CONDITIONS	77	121.5	0.576
24B	VOMITING	5	130.0	0.595
16A	LETHARGY	45	124.4	0.596
26A	ASTHMA	6	125.2	0.634
24A	NAUSEA	3	128.0	0.639
22D	TREMOR + SWEATING	15	125.6	0.684
5A	TALLNESS	63	121.8	0.712
22C	TREMOR/SWEATING	1	113.0	0.742
17A	ALOPECIA	21	123.3	0.743
6A	TACCHYCARDIA	12	121.3	0.794
6B	ARRHYTHMIAS	19	123.3	0.801
22A	TREMOR	8	122.1	0.805
19A	CONSTIPATION	10	123.7	0.819
4F	THINNESS	5	125.8	0.823
14C	NOONAN'S DISEASE	10	122.8	0.831
6C	ALL HEART DISEASE	25	121.9	0.848
4E	EATING DISORDER/DISTURBANCE	6	119.2	0.860
10B	ANAEMIA	7	119.4	0.876
10D	HYPERTENSION	4	122.5	0.897
11C	SELECTED PSYCHOLOGICAL DISORDERS	11	121.1	0.903
13B	CONGENITAL ADRENAL HYPERPLASIA	19	121.7	0.918
4H	COELIAC DISEASE	2	120.5	0.983
16D	LETHARGY + WEAKNESS + MALAISE	53	122.9	0.984

Thirteen diagnostic groups of interest from Table 4.2 were then selected for further analysis. The eight remaining diagnostic groups not selected for further analysis were not analysed due to small sample sizes in some cases, making statistical analysis unfeasible or because the disease giving the significant result in these groups was selected for separate analysis. For example, group 13C (all non-thyroidal endocrine disorders) contained Growth Hormone Deficiency (GHD) as one of its members which was responsible for the significant result in this group. Hence GHD was analysed as a separate diagnostic group (13A) in the study.

The Selected Diabetes, Thalassaemia, Growth Hormone Deficiency, Anorexia Nervosa, Acute Lymphoblastic Leukaemia, All Psychological Disorders and Cystic Fibrosis diagnostic groups showed a significantly low T_4 compared to the control group. The Obesity, Deafness, Failure to Thrive, Slipped Epiphyses, Turner's Syndrome and Juvenile Chronic Arthritis diagnostic groups showed a significantly high T_4 compared to the control group. These groups selected for analysis were further investigated for differences in TSH and T_3U levels and these results are presented in Tables 4.4 to 4.6.

Table 4.4 **T4: Statistical results by diagnostic group**

Ref	Group	Number per group	Mean Difference in T4	p-value
1	SHORT STATURE (control) Mean T4 = 122.6 nmol/L	1155	0.0	-
	Significantly low T4			
2B	SELECTED DIABETES	462	6.2	0
10A	THALASSAEMIA	52	9.5	0.001
13A	GROWTH HORMONE DEFICIENCY	50	8.6	0.002
4D	ANOREXIA NERVOSA	17	18.1	0.003
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	20	15.9	0.003
11D	ALL PSYCHOLOGICAL DISORDERS	18	11.7	0.020
4B	CYSTIC FIBROSIS	32	10.0	0.037
	Significantly high T4			
3A	OBESITY	174	-6.2	0
18	DEAFNESS	25	-15.2	0
4A	FAILURE TO THRIVE	46	-11.4	0.001
20B	SLIPPED EPIPHYSES	9	-15.7	0.009
14A	TURNER'S SYNDROME	47	-7.2	0.011
9A	JUVENILE CHRONIC ARTHRITIS	8	-23.3	0.012

Table 4.5 **TSH: Statistical results by diagnostic group**

Ref	Group	Number per group	Mean Difference in TSH	p-value
1	SHORT STATURE (control) Mean TSH = 2.75 mU/L	1117	0.0	-
	Significantly low T4			
2B	SELECTED DIABETES	443	0.49	0
10A	THALASSAEMIA	48	-0.37	0.071
13A	GROWTH HORMONE DEFICIENCY	47	0.05	0.786
4D	ANOREXIA NERVOSA	14	0.39	0.407
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	18	-0.72	0.109
11D	ALL PSYCHOLOGICAL DISORDERS	10	0.74	0.088
4B	CYSTIC FIBROSIS	28	-0.73	0.003
	Significantly high T4			
3A	OBESITY	139	0.10	0.586
18	DEAFNESS	4	0.60	0.503
4A	FAILURE TO THRIVE	24	-3.29	0.055
20B	SLIPPED EPIPHYSES	6	-0.88	0.170
14A	TURNER'S SYNDROME	44	-0.70	0.002
9A	JUVENILE CHRONIC ARTHRITIS	5	0.61	0.012

Table 4.6 **T3U: Statistical results by diagnostic group**

Ref	Group	Number per group	Mean Difference in T3U	p-value
1	SHORT STATURE (control) Mean T3U = 0.97	1155	0.0	-
	Significantly low T4			
2B	SELECTED DIABETES	462	-0.04	0
10A	THALASSAEMIA	52	-0.03	0.008
13A	GROWTH HORMONE DEFICIENCY	49	0.01	0.683
4D	ANOREXIA NERVOSA	17	0.00	0.778
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	20	-0.03	0.603
11D	ALL PSYCHOLOGICAL DISORDERS	18	-0.01	0.286
4B	CYSTIC FIBROSIS	32	-0.01	0.483
	Significantly high T4			
3A	OBESITY	174	0.04	0
18	DEAFNESS	25	0.01	0.459
4A	FAILURE TO THRIVE	46	0.00	0.975
20B	SLIPPED EPIPHYSES	9	0.03	0.134
14A	TURNER'S SYNDROME	47	-0.01	0.841
9A	JUVENILE CHRONIC ARTHRITIS	8	-0.03	0.190

The above groups were sub-stratified by sex and age (pre- and post-puberty groups) and re-tested. These results are presented below in Tables 4.7 to 4.9 and 4.10 to 4.12 respectively. For T_4, the following diagnostic groups were significant when stratified by sex and age:

- Acute Lymphoblastic Leukaemia, except for females;
- Growth Hormone Deficiency, the Psychological Disorders and Slipped Epiphyses groups, except for the female and pre-pubertal subgroups in each;
- Failure to Thrive, except for female and post-pubertal subgroups;
- Juvenile Chronic Arthritis, except for male and post-pubertal subgroups;
- Selected Diabetes and Thalassaemia, except for the pre-pubertal subgroup in each;
- Cystic Fibrosis, only in females;
- Obesity, only in the pre-pubertal subgroup;

In Anorexia Nervosa and Turner's Syndrome, there were no males, and only the post-pubertal subgroups were significant for each. In the Deafness group, there was no post-pubertal subgroup, with all other Deafness subgroups significant for T_4. As these "missing" data are potential sex and puberty confounders, the stratified groups were tested against the respective Short Stature sub-groups, e.g. Turner's Syndrome (all females) was tested against Short Stature females. The results are presented in Table 4.13.

Table 4.7 **T4: Statistical results by diagnosis and sex**

Ref	Group	Number per group		Mean Difference in T4		p - value	
		M	F	M	F	M	F
1	SHORT STATURE (control) Mean T4 (nmol/L): Males: 120.6 Females: 126.8	781	374	0.0	0.0	-	-
	Significantly low T4						
2B	SELECTED DIABETES	211	251	5.9	9.0	0	0
10A	THALASSAEMIA	20	32	12.8	10.5	0.004	0.012
13A	GROWTH HORMONE DEFICIENCY	35	15	13.5	-3.3	0	0.897
4D	ANOREXIA NERVOSA	0	17	-	22.3	-	0.001
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	14	6	17.7	11.3	0.001	0.510
11D	ALL PSYCHOLOGICAL DISORDERS	10	8	17.8	5.8	0.003	0.606
4B	CYSTIC FIBROSIS	14	18	8.5	13.9	0,246	0.028
	Significantly high T4						
3A	OBESITY	60	114	-5.4	-3.5	0.096	0.071
18	DEAFNESS	13	12	-17.3	-11.0	0.001	0.040
4A	FAILURE TO THRIVE	21	25	-11.2	-9.0	0.024	0.077
20B	SLIPPED EPIPHYSES	4	5	-20.7	-9.2	0.036	0.230
14A	TURNER'S SYNDROME	0	47	-	-3.0	-	0.242
9A	JUVENILE CHRONIC ARTHRITIS	4	4	-6.9	-37.5	0.406	0.008

Table 4.8 **TSH: Statistical results by diagnosis and sex**

Ref	Group	Number per group		Mean Difference in TSH		p - value	
		M	F	M	F	M	F
1	SHORT STATURE (control) Mean TSH (mU/L): Males: 2.76 Females: 2.73	762	355	0.0	0.0	-	-
	Significantly low T4						
2B	SELECTED DIABETES	203	240	0.37	0.59	0	0
10A	THALASSAEMIA	19	29	-0.15	-0.53	0.631	0.045
13A	GROWTH HORMONE DEFICIENCY	33	14	0.16	-0.21	0.552	0.723
4D	ANOREXIA NERVOSA	0	14	-	0.37	-	0.479
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	12	6	-0.40	-1.37	0.485	0.067
11D	ALL PSYCHOLOGICAL DISORDERS	4	6	-0.19	1.35	0.736	0.013
4B	CYSTIC FIBROSIS	13	15	-0.44	-0.99	0.183	0.004
	Significantly high T4						
3A	OBESITY	52	87	0.25	-0.01	0.211	0.672
18	DEAFNESS	3	1	0.33	1.43	0.883	0.265
4A	FAILURE TO THRIVE	12	12	-0.58	-0.51	0.107	0.241
20B	SLIPPED EPIPHYSES	1	5	1.16	1.69	0.505	0.057
14A	TURNER'S SYNDROME	0	44	-	-0.72	-	0.002
9A	JUVENILE CHRONIC ARTHRITIS	3	2	1.36	-0.52	0.061	0.496

Table 4.9 **T3U: Statistical results by diagnosis and sex**

Ref	Group	Number per group		Mean Difference in T3U		p - value	
		M	F	M	F	M	F
1	SHORT STATURE (control) Mean T3U: Males: 0.97 Females: 0.96	781	374	0.0	0.0	-	-
	Significantly low T4						
2B	SELECTED DIABETES	211	251	-0.06	-0.03	0	0
10A	THALASSAEMIA	20	32	-0.06	-0.02	0.001	0.509
13A	GROWTH HORMONE DEFICIENCY	34	15	0.01	-0.02	0.935	0.536
4D	ANOREXIA NERVOSA	0	17	-	0.00	-	0.647
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	14	6	-0.03	-0.01	0.286	0.455
11D	ALL PSYCHOLOGICAL DISORDERS	10	8	-0.03	0.01	0.083	0.749
4B	CYSTIC FIBROSIS	14	18	0.01	-0.02	0.574	0.098
	Significantly high T4						
3A	OBESITY	60	114	0.04	0.04	0	0
18	DEAFNESS	13	12	-0.02	0.04	0.212	0.016
4A	FAILURE TO THRIVE	21	25	-0.01	0.01	0.545	0.726
20B	SLIPPED EPIPHYSES	4	5	0.05	0.01	0.084	0.721
14A	TURNER'S SYNDROME	0	47	-	-0.01	-	0.972
9A	JUVENILE CHRONIC ARTHRITIS	4	4	-0.05	0.00	0.059	0.998

Table 4.10 **T4: Statistical results by diagnosis and puberty**

Ref	Group	Number per group		Mean Difference in T4		p - value	
		3-11 yrs	>11-18 yrs	3-11 yrs	>11-18 yrs	3-11 yrs	>11-18 yrs
1	SHORT STATURE (control) Mean T4 (nmol/L): 3-11 yrs: 124.6 >11-18 yrs: 120.0	662	493	0.0	0.0	-	-
	Significantly low T4						
2B	SELECTED DIABETES	155	307	2.4	6.6	0.414	0
10A	THALASSAEMIA	37	15	5.5	21.9	0.135	0
13A	GROWTH HORMONE DEFICIENCY	22	28	4.6	10.7	0.299	0.001
4D	ANOREXIA NERVOSA	4	13	-4.7	23.1	0.848	0.001
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	12	8	13.8	19.4	0.047	0.019
11D	ALL PSYCHOLOGICAL DISORDERS	4	14	21.3	6.9	0.047	0.213
4B	CYSTIC FIBROSIS	12	20	9.4	9.0	0.231	0.131
	Significantly high T4						
3A	OBESITY	87	87	-10.9	-2.2	0	0.225
18	DEAFNESS	25	0	-13.2	-	0	-
4A	FAILURE TO THRIVE	38	8	-12.5	0.6	0.001	0.742
20B	SLIPPED EPIPHYSES	1	8	-3.4	-19.6	0.918	0.003
14A	TURNER'S SYNDROME	26	21	-5.2	-9.8	0.161	0.024
9A	JUVENILE CHRONIC ARTHRITIS	5	3	-32.2	-7.7	0.008	0.490

Table 4.11 **TSH: Statistical results by diagnosis and puberty**

Ref	Group	Number per group		Mean Difference in TSH		p - value	
		3-11 yrs	>11-18 yrs	3-11 yrs	>11-18 yrs	3-11 yrs	>11-18 yrs
1	SHORT STATURE (control) Mean TSH (mU/L): 3-11 yrs: 2.83 >11-18 yrs: 2.66	635	482	0.0	0.0	-	-
	Significantly low T4						
2B	SELECTED DIABETES	149	294	0.34	0.50	0.005	0
10A	THALASSAEMIA	34	14	-0.04	-1.09	0.643	0.016
13A	GROWTH HORMONE DEFICIENCY	20	27	0.13	-0.05	0.547	0.756
4D	ANOREXIA NERVOSA	4	10	-0.42	0.65	0.338	0.111
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	10	8	-0.63	-0.83	0.369	0.154
11D	ALL PSYCHOLOGICAL DISORDERS	4	6	0.65	0.76	0.449	0.115
4B	CYSTIC FIBROSIS	10	18	-0.41	-0.96	0.262	0.002
	Significantly high T4						
3A	OBESITY	70	69	0.03	0.14	0.976	0.536
18	DEAFNESS	4	0	0.68	-	0.427	-
4A	FAILURE TO THRIVE	18	6	-0.50	-0.53	0.109	0.480
20B	SLIPPED EPIPHYSES	1	5	-2.97	-0.55	0.069	0.369
14A	TURNER'S SYNDROME	24	20	-0.85	-0.52	0.005	0.141
9A	JUVENILE CHRONIC ARTHRITIS	2	3	-0.42	1.26	0.591	0.072

Table 4.12 **T3U: Statistical results by diagnosis and puberty**

Ref	Group	Number per group		Mean Difference in T3U		p - value	
		3-11 yrs	>11-18 yrs	3-11 yrs	>11-18 yrs	3-11 yrs	>11-18 yrs
1	SHORT STATURE (control) Mean T3U: 3-11 yrs: 0.96 >11-18 yrs: 0.97	662	493	0.0	0.0	-	-
	Significantly low T4						
2B	SELECTED DIABETES	155	307	-0.05	-0.04	0	0
10A	THALASSAEMIA	37	15	-0.02	-0.06	0.060	0.025
13A	GROWTH HORMONE DEFICIENCY	21	28	0.02	0.01	0.569	0.817
4D	ANOREXIA NERVOSA	4	13	0.00	0.01	0.743	0.939
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	12	8	-0.04	0.00	0.230	0.502
11D	ALL PSYCHOLOGICAL DISORDERS	4	14	0.01	-0.01	0.988	0.307
4B	CYSTIC FIBROSIS	12	20	0.02	-0.02	0.441	0.186
	Significantly high T4						
3A	OBESITY	87	87	0.04	0.06	0	0
18	DEAFNESS	25	0	0.00	-	0.634	-
4A	FAILURE TO THRIVE	38	8	0.01	-0.03	0.678	0.146
20B	SLIPPED EPIPHYSES	1	8	-0.02	0.04	0.908	0.054
14A	TURNER'S SYNDROME	26	21	-0.02	0.01	0.490	0.257
9A	JUVENILE CHRONIC ARTHRITIS	5	3	-0.02	-0.43	0.541	0.167

Table 4.13 **Analysis of possible sub-group confounding**

Ref	Group	Number per group	Mean difference in T4	p - value
1	**SHORT STATURE (control) - females** Mean T4 = 117.8 nmol/L	251	-	-
4D	ANOREXIA NERVOSA	17	13.3	0.001
14A	TURNER'S SYNDROME	47	-12.0	0.241
1	**SHORT STATURE (control) - 3-11 years** Mean T4 = 124.6 nmol/L	662	-	-
18	DEAFNESS	25	-13.2	0.001

In Table 4.13, the Anorexia Nervosa diagnostic group showed a significantly lower T_4 compared to control group females. Turner's Syndrome was not significantly different from the control group females. The Deafness diagnostic group showed a significantly higher T_4 compared to the pre-pubertal control group. These results are discussed more fully within each diagnostic group in Chapter 6.

Odds Ratio

An odds ratio calculation was used in order to assess the risk of having a low or high T_4 with these diseases. Odds ratios were calculated for T_4 values only, as T_3U and TSH had relatively small sample sizes in particular sub-group analyses. The results of median and quartile odds ratios calculations are presented in Tables 4.14 and 4.15. As in all epidemiological studies, these results do not prove a causal relationship exists between T_4 and the diagnostic groups studied. The odds ratios estimate the probability of having either a high or low T_4 for each disease, compared to the control group. These results *do not* indicate that a low or high T_4 leads to any of these diseases. The 95% confidence interval means that there is a 95% chance that this estimate lies within the given range. Many of the estimates have wide confidence intervals, indicating that the true odds ratio is very difficult to estimate. Where no result is given, the odds ratio could not be calculated due to a zero value in the formula (see Chapter 2), probably because of small sample sizes in some of the quartile splits.

Table 4.14 **T4: Odds Ratios and 95% Confidence Intervals - Median Split**

Ref	Group	Number per group	OR	95% C.I.
1	SHORT STATURE (control)	1155	1.00	-
	Significantly low T4			
2B	SELECTED DIABETES	462	1.46	(1.16 - 1.83)
10A	THALASSAEMIA	52	2.32	(1.23 - 4.41)
13A	GROWTH HORMONE DEFICIENCY	50	2.40	(1.25 - 4.66)
4D	ANOREXIA NERVOSA	17	3.09	(0.92 - 11.41)
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	20	3.09	(1.04 - 9.78)
11D	ALL PSYCHOLOGICAL DISORDERS	18	2.06	(0.71 - 6.19)
4B	CYSTIC FIBROSIS	32	1.97	(0.89 - 4.39)
	Significantly high T4			
3A	OBESITY	174	1.80	(1.27 - 2.54)
18	DEAFNESS	25	5.58	(1.82 - 19.16)
4A	FAILURE TO THRIVE	46	2.22	(1.13 - 4.42)
20B	SLIPPED EPIPHYSES	9	7.77	(0.99 - 166.12)
14A	TURNER'S SYNDROME	47	2.07	(1.07 - 4.05)
9A	JUVENILE CHRONIC ARTHRITIS	8	6.80	(0.84 - 147.46)

Table 4.15 **T4: Odds Ratios and 95% Confidence Intervals - Quartile Split**

Ref	Group	Number per group	OR	95% C.I.
1	SHORT STATURE (control)	1155	1.00	-
	Significantly low T4			
2B	SELECTED DIABETES	462	2.34	(1.67 - 3.27)
10A	THALASSAEMIA	52	3.33	(1.40 - 8.15)
13A	GROWTH HORMONE DEFICIENCY	50	2.96	(1.29 - 6.95)
4D	ANOREXIA NERVOSA	17	4.79	(0.96 - 32.35)
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	20	10.64	(1.40 - 223.62)
11D	ALL PSYCHOLOGICAL DISORDERS	18	4.79	(0.96 - 32.35)
4B	CYSTIC FIBROSIS	32	2.13	(0.73 - 6.45)
	Significantly high T4			
3A	OBESITY	174	1.69	(1.06 - 2.70)
18	DEAFNESS	25	7.52	(1.64 - 47.75)
4A	FAILURE TO THRIVE	46	3.13	(1.17 - 8.85)
20B	SLIPPED EPIPHYSES	9	-	-
14A	TURNER'S SYNDROME	47	2.00	(0.80 - 5.13)
9A	JUVENILE CHRONIC ARTHRITIS	8	-	-

Sub-stratification by puberty and sex

The Short Stature (control) pre- and post-puberty groups, further sub-stratified by sex are presented in Table 4.16 below. The results of the Obesity and Failure to Thrive pre- and post-puberty groups, further sub-stratified by sex and compared to the control group, are presented in Tables 4.17 to 4.18 below.

For both the Failure to Thrive and Obesity groups, significant T_4 results were noted in the pre-puberty groups for both males and females. Although the TSH result for Failure to Thrive approached significance in the total group, this was lost upon sub-stratification. In the Obesity group, TSH was not significant in either of the subgroups or in the whole group.

Table 4.16
Short Stature: sub-analysis by puberty and sex

Sub-group	Number per group	% total	Mean	Standard Deviation
T4				
Males 3-11 yrs	427	37.0%	122.6	21.02
Males >11-18 yrs	354	30.6%	118.2	19.62
Females 3-11 yrs	235	20.3%	128.1	21.27
Females >11-18 yrs	139	12.0%	124.5	23.40
Group total	1155	100%	122.6	21.23
TSH				
Males 3-11 yrs	414	37.1%	2.85	1.49
Males >11-18 yrs	348	31.2%	2.66	1.45
Females 3-11 yrs	221	19.8%	2.79	1.59
Females >11-18 yrs	134	12.0%	2.63	1.40
Group total	1117	100%	2.75	1.49
T3U				
Males 3-11 yrs	427	37.0%	0.96	0.07
Males >11-18 yrs	354	30.6%	0.97	0.07
Females 3-11 yrs	235	20.3%	0.96	0.06
Females >11-18 yrs	139	12.0%	0.97	0.06
Group total	1155	100%	1.01	0.07

Table 4.17
Failure to thrive: sub-analysis by puberty and sex

Sub-group	Number per group	% total	Mean	Standard Deviation	p - value
T4					
Males 3-11 yrs	17	37.0%	134.0	22.10	0.033
Males >11-18 yrs	4	8.7%	122.5	26.89	0.833
Females 3-11 yrs	21	45.7%	139.6	21.70	0.039
Females >11-18 yrs	4	8.7%	116.3	22.22	0.386
Group total	46	100.0%	134.0	22.77	0.001
TSH					
Males 3-11 yrs	9	37.5%	3.36	1.11	0.206
Males >11-18 yrs	3	12.5%	3.30	2.00	0.534
Females 3-11 yrs	9	37.5%	3.30	1.60	0.280
Females >11-18 yrs	3	12.5%	3.07	2.56	0.711
Group total	24	100.0%	3.29	1.50	0.055

Table 4.18
Obesity: sub-analysis by sex and puberty

Sub-group	Number per group	% total	Mean	Standard Deviation	p - value
T4					
Males 3-11 yrs	23	13.2%	136.1	24.21	0.009
Males >11-18 yrs	37	21.3%	119.7	23.52	0.731
Females 3-11 yrs	64	36.8%	135.2	19.17	0.017
Females >11-18 yrs	50	28.7%	124.0	19.69	0.729
Group total	174	100%	128.8	21.90	0
TSH					
Males 3-11 yrs	19	13.7%	2.77	1.42	0.916
Males >11-18 yrs	33	23.7%	2.36	1.38	0.206
Females 3-11 yrs	51	36.7%	2.81	1.44	0.769
Females >11-18 yrs	36	25.9%	2.66	1.35	0.709
Group total	139	100%	2.66	1.40	0.586

CHAPTER 5

RESULTS

PATIENTS AGED LESS THAN 3 YEARS OF AGE

The main diagnoses encountered in patients aged less than 3 years are presented in Tables 5.1 and 5.2 and in Figures 5.1 to 5.12 on the following pages. For each diagnostic group are graphed:

a) The number of cases per age group by diagnostic group, and

b) The mean T_4 per age group by diagnostic group.

Selection of a control group

The Short Stature group (Figures 5.3a and 5.3b) was clearly an inappropriate control group for patients aged less than 3 years, as there was an uneven distribution of patients in this diagnostic group.

Conclusions

The type and frequency diagnoses encountered in patients aged less than 3 years was different to those in the 3-11 years age group (Appendix F). Further work is required to define the characteristics of each of the diagnostic groups for patients aged less than 3 years. This would be feasible only after the identification of a suitable control group for these patients.

Table 5.1 **Patients aged < 3 years: Number per age group by diagnostic group**

Age Group	Number per group											
	Failure to Thrive	**Jaundice**	**Short Stature**	**Developmental Delay**	**Deafness**	**Constipation**	**Hydronephrosis**	**Down's Syndrome**	**IDDM**	**Slow Growth**	**Precocious Puberty**	**Prematurity**
0 - 2 wks	1	58	0	0	0	0	1	0	0	0	0	3
>2 - 4 wks	11	50	0	2	0	3	1	1	0	0	0	3
>4 - 6 wks	3	32	0	0	0	0	0	0	0	0	0	0
>6 - 8 wks	14	16	1	1	0	2	3	0	0	0	0	0
>2 -3 mths	17	8	1	2	1	6	1	0	0	0	0	3
>3 - 4 mths	8	2	0	1	0	1	1	0	0	0	0	0
>4 - 6 mths	14	0	1	8	2	5	5	1	0	0	0	0
>6 - 9 mths	25	0	8	10	2	3	3	1	1	2	1	0
>9 - 12 mths	29	0	17	20	2	1	3	2	1	1	2	1
>1 - 2 yrs	56	1	51	29	17	10	3	7	6	4	5	0
>2 - <3 yrs	20	0	42	14	13	2	0	4	7	5	2	0

Table 5.2 **Patients aged < 3 years: Mean T4 per age group by diagnostic group**

Age Group	Mean T4 (nmol/L)											
	Failure to Thrive	**Jaundice**	**Short Stature**	**Developmental Delay**	**Deafness**	**Constipation**	**Hydronephrosis**	**Down's Syndrome**	**IDDM**	**Slow Growth**	**Precocious Puberty**	**Prematurity**
0 - 2 wks	289.0	167.3	-	-	-	-	253.0	-	-	-	-	111.7
>2 - 4 wks	174.9	157.1	-	160.0	-	180.7	215.0	98.0	-	-	-	155.3
>4 - 6 wks	189.3	154.8	-	-	-	-	-	-	-	-	-	-
>6 - 8 wks	162.6	146.3	124.0	163.0	-	160.5	174.0	-	-	-	-	-
>2 -3 mths	161.5	162.3	102.0	157.5	191.0	172.7	204.0	-	-	-	-	225.7
>3 - 4 mths	163.8	158.0	-	163.0	-	167.0	171.0	-	-	-	-	-
>4 - 6 mths	132.4	-	147.0	159.8	196.5	156.6	154.6	166.0	-	-	-	-
>6 - 9 mths	133.6	-	139.8	144.1	112.5	111.3	155.0	210.0	128.0	129.0	136.0	-
>9 - 12 mths	146.9	-	143.8	122.4	125.5	123.0	126.0	143.0	118.0	128.0	116.5	74.0
>1 - 2 yrs	135.6	201.0	136.5	129.7	135.1	130.3	122.7	139.7	119.2	126.0	164.2	-
>2 - <3 yrs	133.9	-	141.0	141.1	141.2	121.0	-	129.3	129.1	129.0	163.5	-

Figure 5.1a **Failure to Thrive: Number per group**

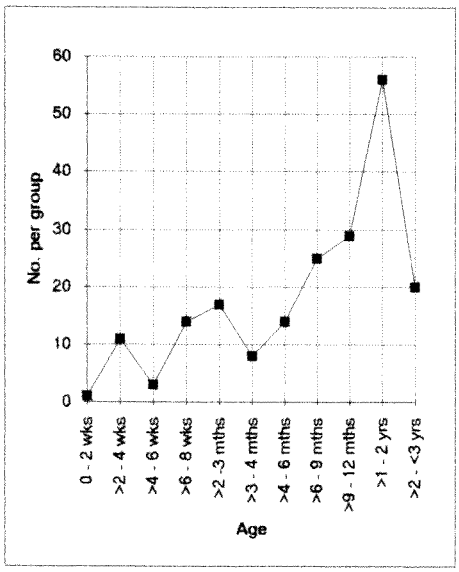


Figure 5.1b **Failure to Thrive: Mean T4 per group**

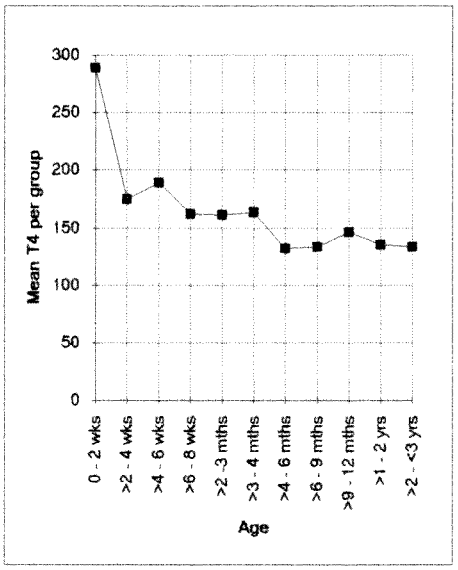


Figure 5.2a **Jaundice: Number per group**

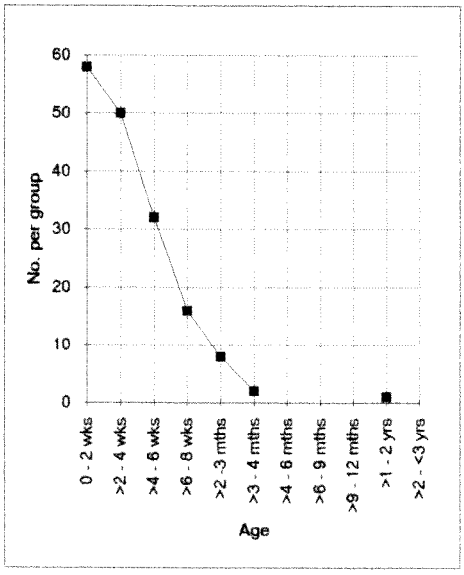


Figure 5.2b **Jaundice: Mean T4 per group**

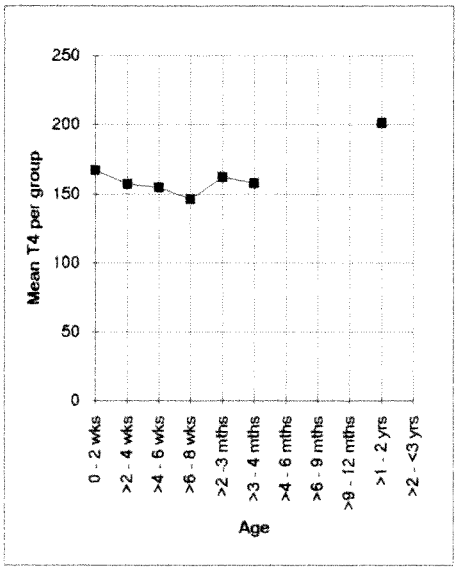


Figure 5.3a **Short Stature: Number per group**

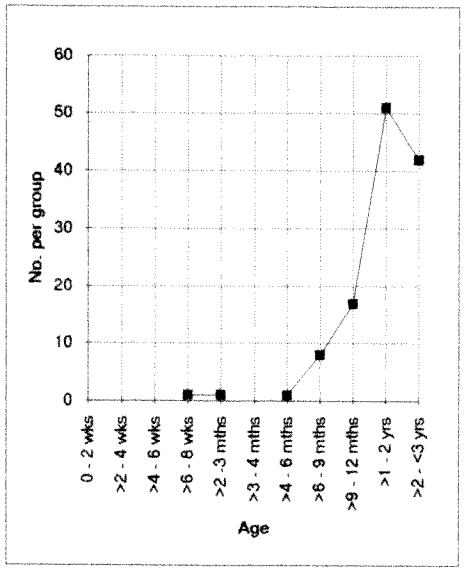


Figure 5.3b **Short Stature: Mean T4 per group**

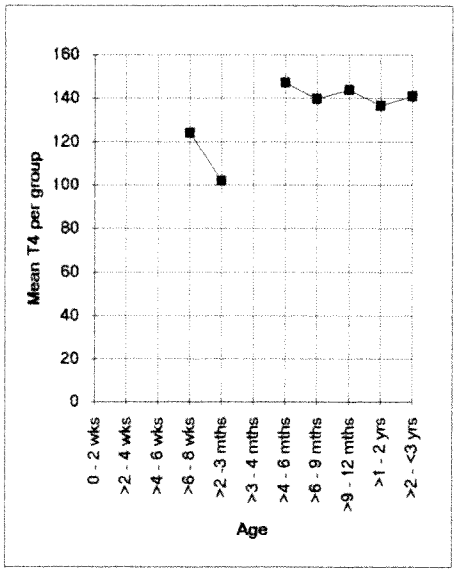


Figure 5.4a **Developmental Delay: Number per group**

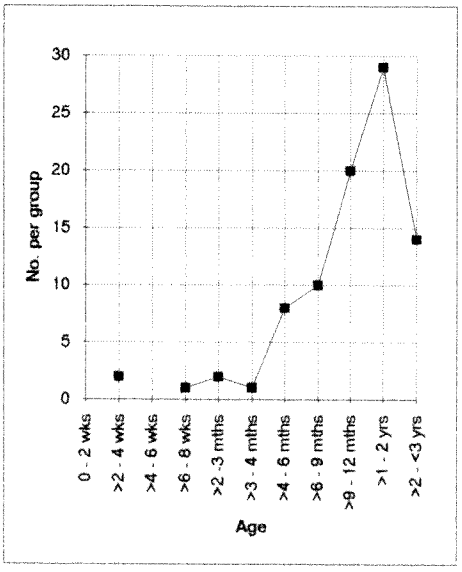


Figure 5.4b **Developmental Delay: Mean T4 per grou**

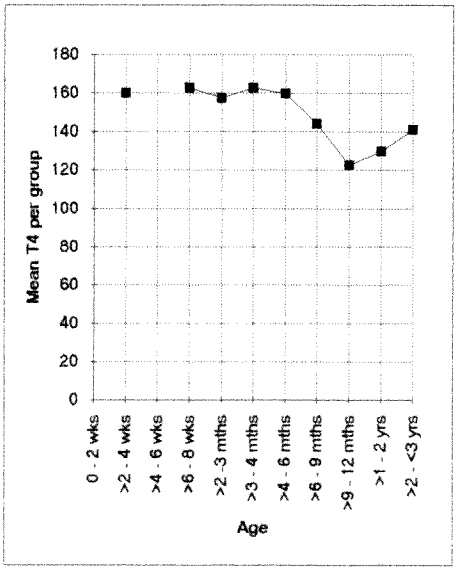


Figure 5.5a **Deafness: Number per group**

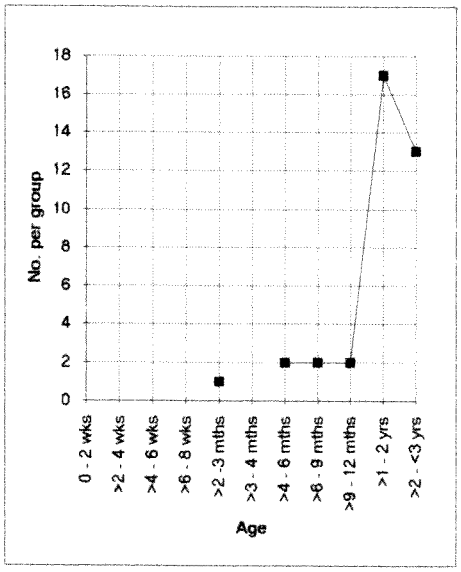


Figure 5.5b **Deafness: Mean T4 per group**

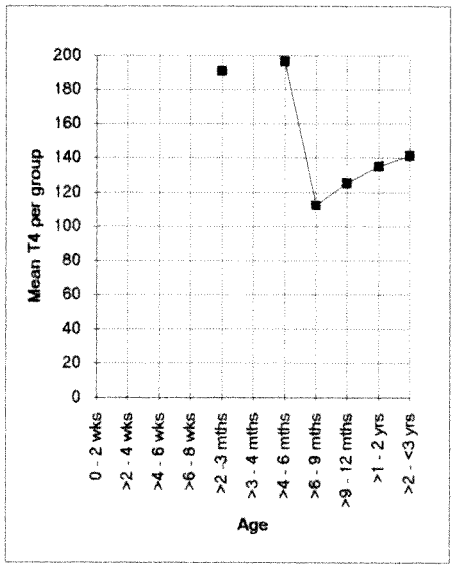


Figure 5.6a **Constipation: Number per group**

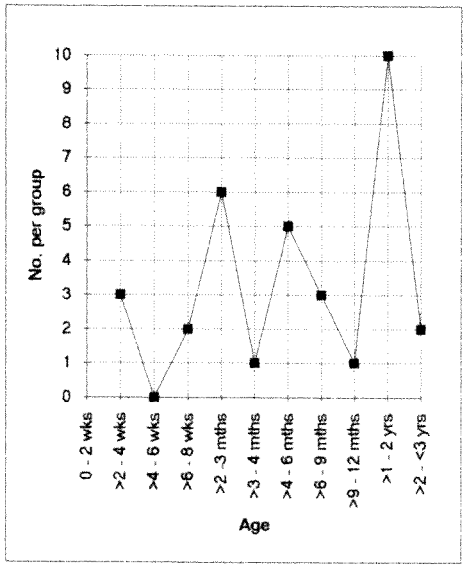


Figure 5.6b **Constipation: Mean T4 per group**

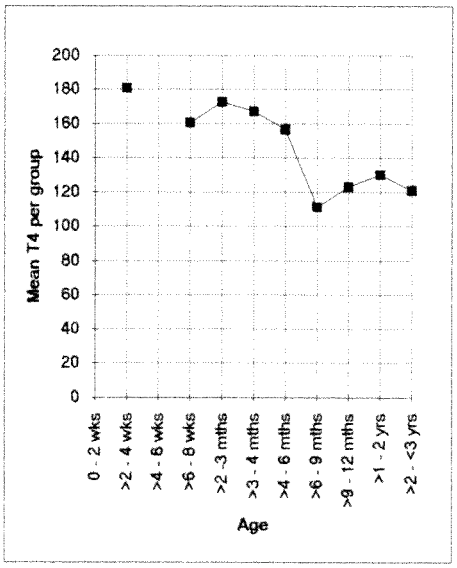


Figure 5.7a **Hydronephrosis: Number per group**

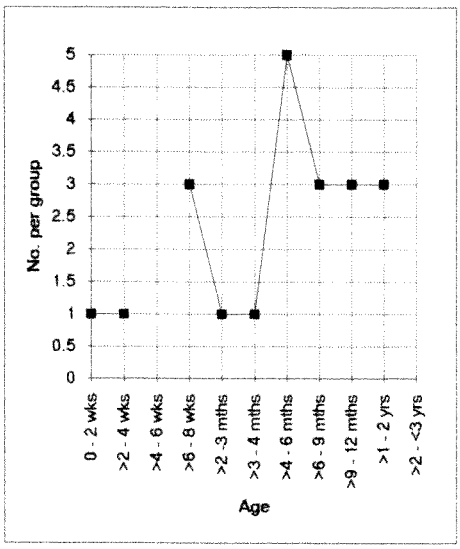


Figure 5.7b **Hydronephrosis: Mean T4 per group**

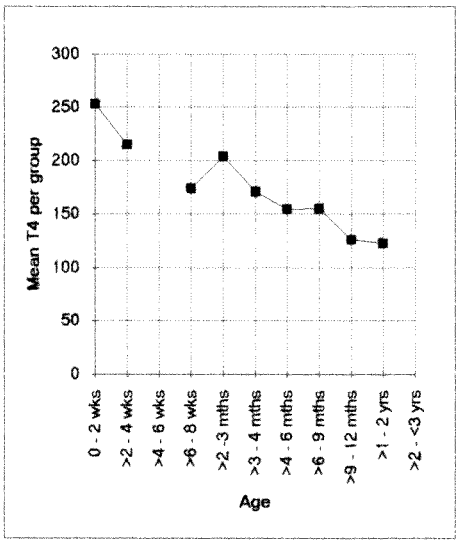


Figure 5.8a **Down's Syndrome: Number per group**

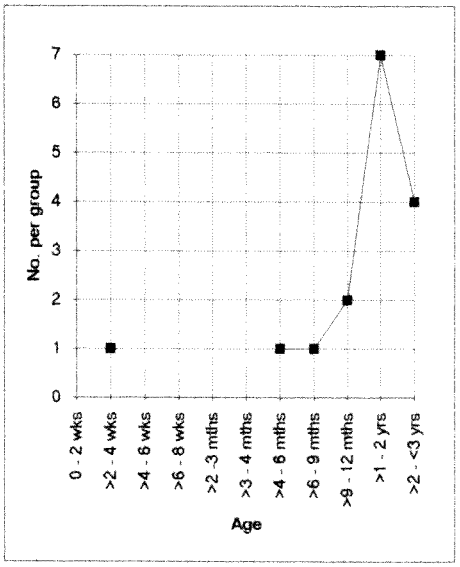


Figure 5.8b **Down's Syndrome: Mean T4 per group**

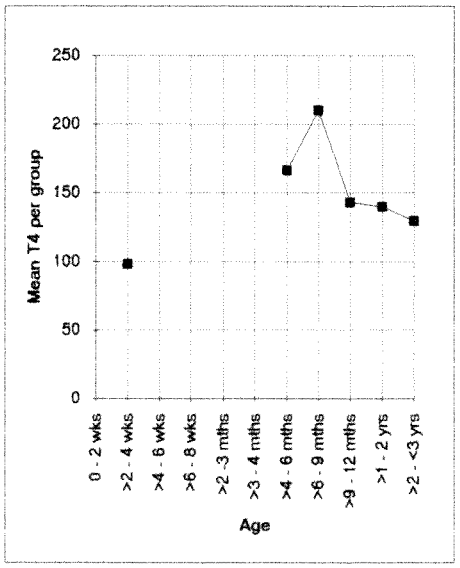


Figure 5.9a **IDDM: Number per group**

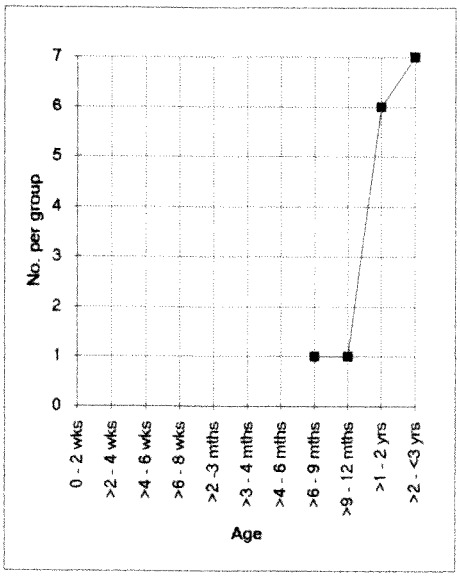


Figure 5.9b **IDDM: Mean T4 per group**

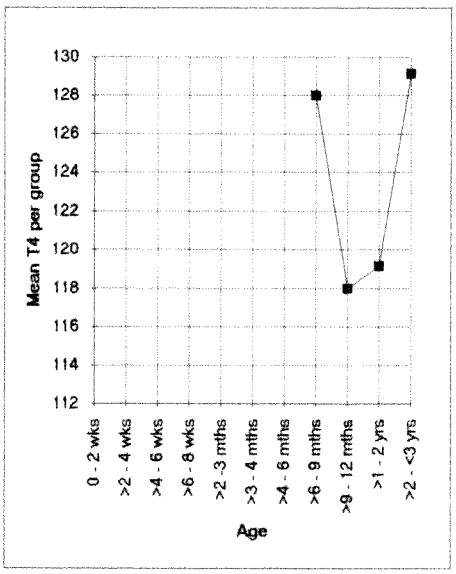


Figure 5.10a **Slow Growth: Number per group**

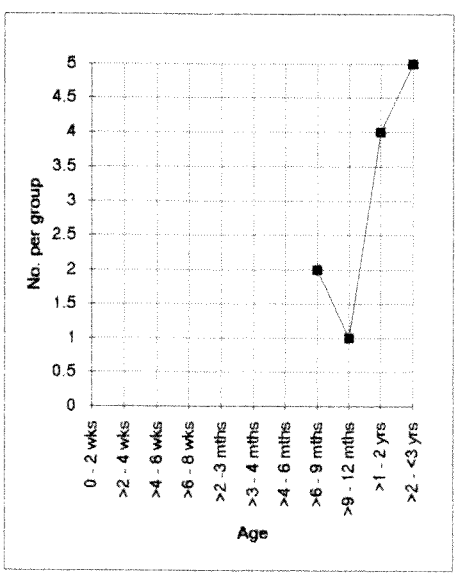


Figure 5.10t **Slow Growth: Mean T4 per group**

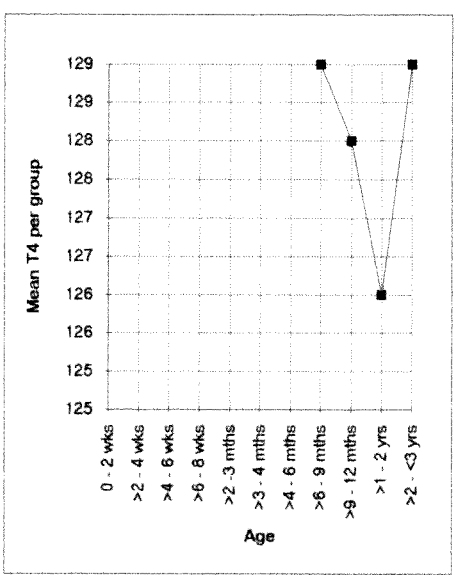


Figure 5.11a **Precocious Puberty: Number per group**

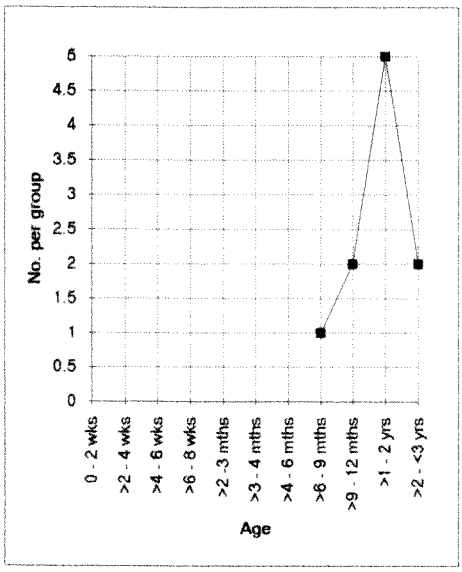


Figure 5.11b **Precocious Puberty: Mean T4 per group**

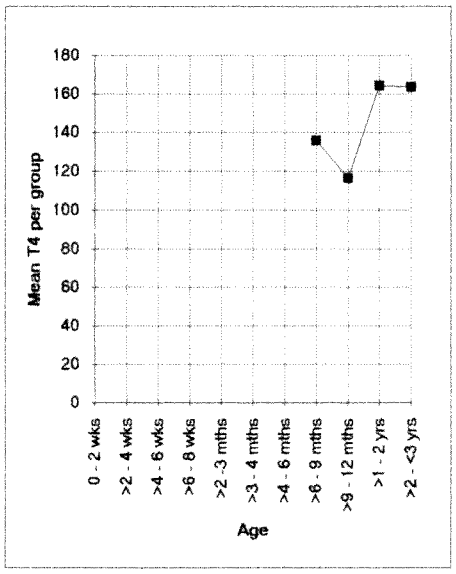


Figure 5.12a **Prematurity: Number per group**

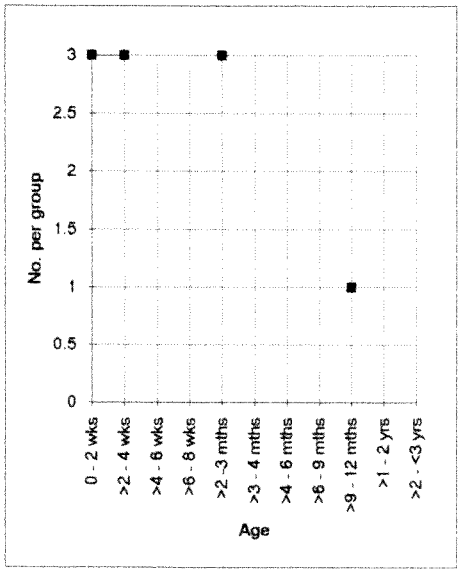
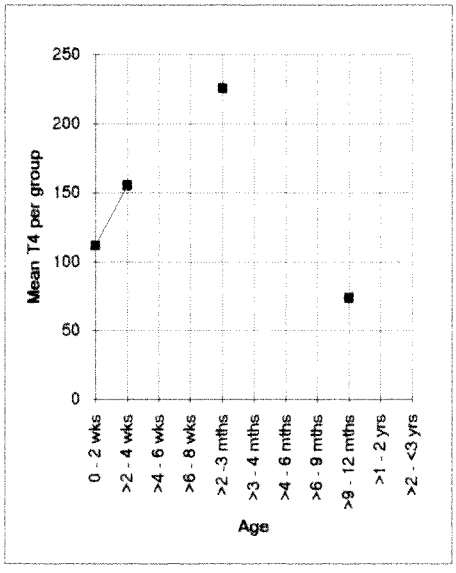


Figure 5.12b **Prematurity: Mean T4 per group**



CHAPTER 6

DISCUSSION

Description of the evidence

The source population was children living in N.S.W. aged 3-18 years of age, attending the RAHC for thyroid function tests between 1980 and 1990 and recorded in the Clinical Biochemistry Department log book. The initial inspection of the raw data found information on different diagnoses and almost complete thyroid function test results for each entry were available.

The relationship between the thyroid function test results for each patient - thyroxine (T_4), thyroid stimulating hormone (TSH) and triiodothyronine uptake, (T_3U) and presenting diagnosis was the basis of our investigation using the format of an epidemiological case-control study. This study type was chosen for analysis as the patients were identified first on disease status and then on exposure (thyroid function).

Hence the study factors for this study were the results of thyroid function tests for T_4, TSH and T_3U, and the outcome factors were the various diagnostic groups investigated. The research question was thus the relationship between thyroid hormone levels and various diagnostic groups in children having thyroid function tests at the RAHC between 1980 and 1990.

The main results are shown below in Tables 6.1 and 6.2 in which are summarised the general results per diagnostic group. The diagnostic groups are presented in two separate categories by the initial findings of a significantly high or low T_4.

Table 6.1 shows the number of patients in each diagnostic group by thyroid function test. Table 6.2 gives for each diagnostic group, median and quartile split odds ratios

for T_4. P-values calculated using the Wilcoxon Rank Sum Test are also included here for each diagnostic group by thyroid function test. Highly significant p-values, ($p < 0.01$) are shown in italics. These should be read in together with the odds ratios given, to more accurately assess the possible relationship between T_4 and diagnostic state.

Table 6.1 **Number of patients per diagnostic group by thyroid function test**

Ref	Group	Number per group		
		T4	**TSH**	**T3U**
1	SHORT STATURE (control)	1155	1117	1155
	Significantly low T4			
2B	SELECTED DIABETES	462	443	462
10A	THALASSAEMIA	52	48	52
13A	GROWTH HORMONE DEFICIENCY	50	47	49
4D	ANOREXIA NERVOSA	17	14	17
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	20	18	20
11D	ALL PSYCHOLOGICAL DISORDERS	18	10	18
4B	CYSTIC FIBROSIS	32	28	32
	Significantly high T4			
3A	OBESITY	174	139	174
18	DEAFNESS	25	4	25
4A	FAILURE TO THRIVE	46	24	46
20B	SLIPPED EPIPHYSES	9	6	9
14A	TURNER'S SYNDROME	47	44	47
9A	JUVENILE CHRONIC ARTHRITIS	8	5	8

Table 6.2 **Summary of results per diagnostic group**

Ref	Group	Odds Ratio on T4		p-values*		
		Median	Quartile	T4	TSH	T3U
1	SHORT STATURE (control)	1.00	1.00	-	-	-
	Significantly low T4					
2B	SELECTED DIABETES	1.46	2.34	*0*	*0*	*0*
10A	THALASSAEMIA	2.32	3.33	*0.001*	0.071	*0.008*
13A	GROWTH HORMONE DEFICIENCY	2.40	2.96	*0.002*	0.786	0.683
4D	ANOREXIA NERVOSA	3.09	4.79	*0.003*	0.407	0.778
15A	ACUTE LYMPHOBLASTIC LEUKAEMIA	3.09	10.64	*0.003*	0.109	0.603
11D	ALL PSYCHOLOGICAL DISORDERS	2.06	4.79	0.020	0.088	0.286
4B	CYSTIC FIBROSIS	1.97	2.13	0.037	*0.003*	0.483
	Significantly high T4					
3A	OBESITY	1.80	1.69	*0*	0.586	*0*
18	DEAFNESS	5.58	7.52	*0*	0.503	0.459
4A	FAILURE TO THRIVE	2.22	3.13	*0.001*	0.055	0.975
20B	SLIPPED EPIPHYSES	7.77	-	*0.009*	0.170	0.134
14A	TURNER'S SYNDROME	2.07	2.00	0.011	*0.002*	0.841
9A	JUVENILE CHRONIC ARTHRITIS	6.80	-	0.012	0.012	0.190

*Numbers in italics are p-values < 0.01

Internal validity

Selection Bias

Selection bias can occur whenever the inclusion of cases or controls into the study depends in some way on the exposure of interest *(Hennekens & Buring, 1987)*. It can be a problem in case-control studies since the diseases have already occurred at the time of subject selection and data on exposure is gathered retrospectively. In this study the exposure is thyroid function and the disease is the list of various diagnostic groups. In an attempt to control for selection bias in this study, patients with known thyroid disease were excluded. In a subset of the population, (letter "A"), 8.9% were excluded for this reason. The majority of the exclusions were to do with inconsistencies in the data. A further analysis could record data on these exclusions i.e. age, sex etc. These excluded groups could then be compared to the study population to check whether they are significantly different and if they are, the conclusions of the study be possibly re-defined.

Measurement bias

Potential measurement bias of the outcome factor in this study include:

(i) The scope for error on the laboratory request form from which the data was entered into the log book.

(ii) The diagnosis listed may be an assumption and possibly inaccurate, e.g. Anorexia nervosa may have been diagnosed as simply just "thin", in which case it was entered as such and not included as part of the anorexia nervosa diagnostic group.

(iii) Scope for error in interpreting handwriting on both the request form and in the log book. This of course, applies to both non-numeric and numeric data. Generally, though, the entries were fairly consistent. Mainly two members of the Clinical Biochemistry Department, RAHC, entered the thyroid function test requests and subsequent results into the log book which was used as the basis for data entry. When in doubt these small number of entries were excluded so the bias was decreased.

Data sorting, the exclusion of duplicate entries and those of unknown sex from the analysis (as detailed in Chapter 2) also helped to control for measurement bias.

Measurement of Study Factor

Radioimmunoassay (RIA) techniques are used by the Clinical Biochemistry Department at the RAHC to test for T_4 and TSH. T_3U is a resin uptake test using $I\text{-}_{125}$ - labelled T_3 and is reported as a ratio, therefore having no units. The *N.M.L.* kit was used to measure total T_4. Total T_4 is no longer routinely done, in favour of free T_4. The *Corning Magic MAB* kit is used to measure TSH. The total T_4, TSH and T3U tests all use *N.M.L. Thyrotrol* as a control.

A varying mean T_4 per year over 1980 to 1990 was noted in the total study population (Figure 3.3b) and this is most likely due to an operator difference rather than a change in the assay. The RAHC assay method for T_4 did not change over the

period 1980 to 1990. One person performed the assay during 1980 to 1989. From 1990 onwards, another person performed the assay. The control group was also analysed in the same way as the total study population (Figure 3.4b) and the variations were similar over time. It was concluded that this bias would then not affect the case-control analysis.

Confounding

A confounder is any factor which affects exposure and disease simultaneously and if not taken into consideration will lead to erroneous interpretation of the results. Potential confounders identified in this study were thyroid disease, other diseases which affect thyroid function, age, sex, puberty, year of diagnosis (see *Measurement Bias* above) and some of the combined diagnoses. In this study, as exemplified below, inclusion, exclusion, and stratification were strategies used to deal with confounding (Figure 2.3).

Stratification was used to deal with age as this was identified as an *interaction factor* - ie. a factor for which various subsets of the total population are fundamentally different from one another. In this case, the varying normal ranges for thyroxine in patients aged less than and greater than 3 years of age respectively indicate that the two groups are metabolically different and hence not a homogeneous population. Hence the total population was stratified into two categories: patients aged less than 3 years of age and; patients aged 3 to18 years of age.

Sex and puberty were considered confounders since a general review of the data found that differences occurred in the overall data between age and sex with respect to a possible link between T_4 levels and age. This was especially important in pre- and post- puberty groups with a decrease in T_4 post-puberty. Females had a slightly higher T_4 than males in this population also. The data was then stratified by sex and into pre- pubertal (3-11 years) and post-pubertal (>11-18 years) and each analysed

separately for T_4, TSH and T_3U. It is interesting to note that in some cases, although significance was achieved in the total group, this was not the case upon stratification. This is most likely due to the small sample size in some of the stratified groups or may be due to possible interaction effects. As these data are new and preliminary analyses, further adjustment by conditional logistical regression was considered inappropriate, as it was considered important to analyse only crude, or stratified effects.

Precision

With the number of statistical tests (p-values) calculated on the data as in this study, it is likely that some of the results will show a falsely significant result, purely due to chance *(Rothman, 1986)*. Significance testing at the five percent level ($p = 0.05$) means that there will be a 1 in 20 chance of a false positive association. When odds ratios were calculated, in some of the diagnostic groups, there were limited sample sizes, especially in quartile splits, e.g. n=9 for Slipped Epiphyses and n=8 for Juvenile Chronic Arthritis, and thus corresponding wide confidence intervals. Therefore, chance variation in this study cannot be excluded as a possible explanation of the results but looking at a significance level of $p < 0.01$ and quartile versus median splits (Table 6.2) confidence can be gained in the main results.

Methods to deal with the issues of multiple testing include redefining the level of significance testing, either by changing the criterion to a more stringent value, such as 1 per cent instead of 5 per cent, or by actually inflating the calculated p-values by some factor that depends on the number of comparisons made *(Rothman, 1986)*.

Temporal relationships

Case-control studies are commonly weak with respect to time relationships *(Elwood, 1988)*. Due to the nature of the study, no data is available on the condition of the patient before or after the diagnosis listed was made. Duplicate entries were

excluded, keeping only the first chronological entry for each patient. A temporal relationship of thyroid function to disease can therefore not be assessed here.

Strength of the association

When assessing causality in an epidemiological study, the degree to which the risk of thyroid function relating to diagnostic groups is indicated by the calculations of odds ratios. The numerically higher the odds ratio, the greater the probability of an association being causal. In this study, the higher odds ratios tended to have wider confidence intervals and smaller sample sizes (Tables 4.11 and 4.12)

A *dose response* relationship also increases the likelihood of causality as it gives an indication of the consistency of the association in the data. When comparing median and quartile odds ratios, the odds ratio increases from median to quartile split for all except the obesity diagnostic group. This indicates a probability that there is a causal relationship between thyroid function tests and disease in all except the obesity group.

External validity

These results can only be applied to the source population as hypotheses, as they are based on descriptive data and give an indication of a possible association between thyroid function and the different diseases tested in the study population.

Comparison of the results with other evidence

In summary, most of the literature on the diagnostic states investigated, where available, supports the various thyroid function test results for these groups. This is discussed in more detail below by specific diagnostic group.

Biological Causality

Diagnostic states can affect thyroid function in a variety of different ways. Generally, conditions affecting the thyroid gland directly will be reflected in the results for T_4. Conditions which affect the hypothalamic-pituitary axis (HPA), or central mechanism, will be reflected in the results for TSH. Conditions which affect protein-binding mechanisms will be reflected in the results for T_3U, in addition to T_4. These are discussed in more detail below within each diagnostic group.

In the various diagnostic states discussed below, the results of thyroid function testing in the whole diagnostic group are summarised for each of T_4, TSH and T_3U respectively:

H - significantly high result when compared to the control group

L - significantly low result when compared to the control group

N - not significant when compared to the control group

Selected Diabetes (L-L-H)

The diabetes diagnostic group gave the most striking results of any other diagnostic group giving a highly significant result throughout the three parameters tested. On stratification, the only non-significant result was in the T_4 result for patients aged 3-11 years. T_3U was significantly high when compared to the control group so this indicates a reduced number of binding sites on plasma proteins (mainly thyroid binding globulin or TBG) for T_4. Reduced binding sites mean that the carrying capacity of TBG is less and so total T_4 in plasma is lower. In a separate study, it was also found that free T_4 was low in diabetic children. *(Coakley & Earl, 1994).* Although T_4 is low and free T_4 is probably low, this did not lead to a raised TSH (which is the usual response). The usual HPA control mechanism then seems to be impaired, indicating possible damage to the hypothalamus or the pituitary. Some diabetics do go on to develop primary or secondary hypothyroidism, as the

autoimmune process which affects the pancreas can also affect the thyroid or pituitary glands in some patients.

From the literature, diabetes and thyroid function are linked at several levels. Kinetic studies demonstrate a marked reduction in T_4 to T_3 conversion in poorly controlled diabetics *(Pittman, et al 1979a, 1979b, cited in Middlesworth, 1986)* and changes in thyroid hormones levels are also seen in diabetics with ketoacidosis *(Parr, 1987)*.

Thalassaemia (L-N-H)

The results for this diagnostic group show a consistently low T_4 across the total group and upon stratification by sex and puberty. TSH was unaffected, suggesting central receptors are not responding to the reduced T_4 levels. This effect was greatest in the 11-18 years age group. These results indicate a cumulative effect, being greatest in the oldest age group, consistent with damage to the thyroid and/or pituitary gland, as well as reduced or damaged plasma proteins. Free T_4 may be normal, even though total T_4 is reduced. T_3U was significantly higher in this diagnostic group compared to the control group and this result indicates that binding sites on TBG and other proteins are reduced. Although patients on known drug therapy were excluded from this group, drugs used in the treatment of thalassaemia may displace T_4 from the binding sites on TBG.

Thyroid dysfunction has been reported to occur frequently in thalassaemia major, but its prevalence and severity varies in different groups *(Landau et al, 1993)*. Thalassaemia is associated with increasing iron deposition in the endocrine cells and generally with increased prevalence of endocrinopathies. Progression is variable and it may take years to progress from a normal state to hypothyroidism *(Landau et al, 1993)*. As the accumulation of iron takes time to affect the thyroid gland, a marked deficiency in thyroid function occurring in the older age group would be expected. It

is thought that abnormal thyroid function with thalassaemia may be reversible in the early stages *(Landau et al, 1993)*.

Growth Hormone Deficiency (L-N-N)

In this study, GHD patients showed a significantly lower T_4 than the control group. In females and in patients aged 3-11 years, T_4 was not significantly different to the control group. The normal T_3U for all groups, indicated no abnormality with protein binding of T_4. GHD then, appears to affect thyroid function as a central effect. The mechanism leading to low GH from the HPA may also result in a diminished response to low T_4, with TSH not being raised to correct the lower T_4 level. The idiopathic form of GHD may be divided into isolated GHD and multiple pituitary hormone deficiency, with possibly 50 per cent of cases of idiopathic GHD associated with decreased secretion of other pituitary hormones *(Gunn, 1987)*.

Anorexia Nervosa (L-N-N)

A significantly low T_4 was found in the anorexia nervosa diagnostic group (AX) in this study with no difference in T_3U or TSH when compared to the control group. This effect was seen in females and also in the post-puberty group. As the sample contained no males, the AX group was compared to Short Stature females and a significantly low T_4 was found (Table 4.13) as in the total group. Hence sex is not a confounder in this diagnostic group. Anorexia nervosa is more commonly suspected in females and this accounts for the sample profile of this group. It occurs most commonly in post-pubertal females, so these are expected results.

As for GHD above, the results for the AX group tend to indicate an altered central mechanism (i.e. a lack of TSH responsiveness to a low T_4). In anorexia nervosa, a mechanism for lowering T_4 and hence energy expenditure and metabolic rate may operate when energy reserves are reduced. This mechanism may operate at several levels in T_4 formation, including a lack of TSH responsiveness to a low T_4 and

reduced T_4 to T_3 conversion in the tissues. Although a low TSH was not demonstrated in AX compared to the control group, the sample size is relatively small. Also, the RIA assay for TSH used in this study is not particularly sensitive in detecting low TSH levels.

In a study of only ten patients with anorexia nervosa, Kiyohara et al, (1989) also found that basal T_4, T_3 and TSH were significantly lower before weight recovery in patients with anorexia nervosa than they were in control subjects. This supports the findings of the present study. After weight recovery, basal T_4, and TSH levels were unchanged and significantly lower in patients with the disorder. Basal T_3 concentrations increased slightly after weight gain but still remained lower than the control group.

In patients with anorexia nervosa, extremely low levels of serum T_3 are thought to be the result of impaired peripheral conversion of T_4 to T_3, associated with chronic starvation, however, a dysfunctional HPA may also play a role *(Kiyohara et al, 1989)*. It has also been observed that serum TSH levels occasionally conflict with the actual values of circulating thyroid hormones in patients with anorexia nervosa. This also confirms the findings of the present study which did not find a significant increase in TSH as a response to a low T_4.

In a study by Bannai et al (1988), sixteen female patients with anorexia nervosa during self-induced starvation displayed clinical findings suggesting hypothyroidism in association with decreased serum total T_4,and T_3. This result suggests that the peripheral metabolic state of underweight anorexia nervosa sufferers depends considerably on the serum T_3 concentration since, despite decreased total thyroid hormone levels, the free T_4 was normal in five of the sixteen cases examined, *(Kiyohara et al, 1989)*.

Acute Lymphoblastic Leukaemia (L-N-N)

A significantly lower T_4 was noted in this diagnostic group (ALL), in females and separately in pre- and post-puberty groups, but no significant difference was found for T_3U or TSH compared to the control group. It seems likely that some central effect may be occurring here, reducing TSH responsiveness to a low T_4. ALL patients can have growth problems due to their treatment which may affect the body's GH release mechanism. The same process could be affecting TSH responsiveness, similar to the idiopathic form of hypothyroidism. Although patients on known drug therapy were excluded from this group, drugs used in the chemotherapy of ALL patients do not appear to displace T_4 from plasma proteins, as T_3U was unaffected.

Subtle primary hypothyroidism is relatively common in patients with acute lymphoblastic leukaemia, particularly in those who have been treated with craniospinal irradiation *(Pasqualini et al, 1991)*. In the present study, patients who were listed as having radiotherapy were excluded from the analysis. Ferster et al (1992) measured parameters of thyroid function in nine children during induction therapy for ALL. During induction, total T_4 significantly decreased, free T_4, total T_3 and TBG were decreased. During late intensification therapy, significant decreases in T_3 and TBG were observed, but there were no significant changes in T_4 and free T_4. The authors concluded that during induction, the impairment of thyroid function is attributable to L-asparaginase, an enzyme, whereas during late intensification, low T_3 and low TBG is due to glucocorticoid administration.

Psychological Disorders (L-N-N)

The Psychological Disorders diagnostic group in this study is a heterogeneous sample, with a number of disorders grouped to make a single diagnostic group. These disorders were: Anxiety, Behaviour Disorder, Hyperactivity, Depression, Aggression, Bipolar Active Disorder, Confusion and Psychotic Illness.

This group showed a significantly low T_4 in males and in the pre-puberty group, but no significant overall TSH and T_3U effects, except for a significantly low TSH finding in females. The findings are limited by a small sample size, (total n = 18). It is unclear what relationship exists between psychological disorders and altered T_4 metabolism but it should be noted that the AX group above, also a psychological disorder, showed similar trends to the Psychological Disorders diagnostic group.

A variety of severe psychiatric disturbances may be associated with transient alterations in serum thyroid hormone levels, such as elevated serum total and free T_4, variable TSH and normal T_3 concentrations *(Spratt et al, 1982)*. Nowotny et al (1990), investigated the correlation between pathological signs in thyroid disorders and alterations of peripheral thyroid hormones. They found that patients with latent hyperthyroidism were more subject to somatic symptoms and affective complaints than were those who had latent hypothyroidism. As compared with controls, there were significant differences in exhaustion and pain in the limbs and heart and the patients were more depressive, anxious, touchy and irritable; their personalities showing a higher degree of emotional lability, excitement and irritability.

Cystic Fibrosis (L-H-N)

In the Cystic Fibrosis diagnostic group (CF) a significantly low T_4 and a significantly high TSH were found. On stratification, a significantly high TSH was found only in females. The males were not significant, most likely due to the reduction in sample size upon stratification. TSH was also significant in the post-puberty group. T_3U was not significantly different from the control group in any of the stratified groups. This is clearly not a central effect because TSH is responding to the low T_4 levels in the blood. It is also not apparently a protein binding effect because of the normal T_3U result. It may also be that CF which affects all endocrine glands, is having an effect upon either the thyroid gland or upon the turnover of T_4 in the tissues. However,

histological abnormalities of the thyroid gland have been reported in children with cystic fibrosis *(Braverman & Utiger, 1991).*

Obesity (H-N-L)

In this study, the obesity diagnostic group (OW) overall was found to have a significantly high T_4, but TSH was not significantly different from the control group. The result for T_3U was also significantly lower when compared to the control group. The T_4 effect was lost on stratification by sex and only remained significant in the pre-pubertal group. However, sub-stratification by sex and puberty still showed a significantly raised T_4 for both males and females in the 3-11 year age group.

This is very interesting because the findings for the OW group were opposite to the AX group. However, the thyroid hormone biochemistry may be somewhat different here as the OW group showed a significantly lower T_3U level than the control group. The lower T_3U indicates more binding sites are available on plasma proteins and hence T_4 carrying capacity is increased.

In malnutrition, liver protein synthesis is reduced, so it may be that in well nourished individuals protein synthesis, including TBG and other thyroid hormone binding proteins, is increased. This would account for the decreased T_3U level and increased T_4 levels in this group. T_4 regulates the metabolism of lipids and clinically low T_4 levels are often associated with high levels of cholesterol and lipids in the blood.

Just as in anorexia nervosa, where there may be a mechanism limiting energy consumption when energy reserves are low, in obesity, thyroid biochemistry may also play a role in attempting to reduce excess energy reserves. A study by Chomard et al (1985) found that thyroid function is disturbed in moderately obese patients, mainly characterized by low serum total and free T_3 concentrations which may be due to a number of factors.

Deafness (H-N-N)

The deafness diagnostic group in this study showed a significantly high T_4 but there was no significant difference for T_3U and TSH compared to the control group, although sample size was a problem with testing for TSH (n = 4). The results of the analysis were also consistent through stratification for sex. Upon stratification for puberty, it was discovered that the Deafness diagnostic group contained data for patients aged 3-11 years only. This sub-group was tested against the corresponding control group (3-11 years) and a significantly high T_4 was found (Table 4.13) as for the total group. Therefore puberty does not appear to be a confounder in this group.

The occurrence of congenital deafness, mutism and goitre unassociated with cretinism or mental retardation in euthyroid patients is known as Pendred's Syndrome. It has been estimated that 4-10 % of children with congenital deafness suffer from this condition *(Elamin, 1991)*. The perceptive hearing loss is considered to be present at birth although it is frequently not recognized for several years. The goitre becomes apparent in the pre-pubertal years. The thyroid defect has been shown to lead to the underproduction of T_4 and subsequent thyroid hyperplasia, and has an equal incidence in both sexes which is unusual in thyroid disease.

However the present study did not find reduced T_4 but rather raised T_4. The reason for this finding is uncertain but it may be related to a partial lack of responsiveness in the tissues of some patients to thyroid hormones, leading both to hearing loss and a disturbance in T_4 regulation.

Jaffiol et al (1992) suggest that thyroid hormone resistance in children may affect some or all tissues. The generalized resistance is an inherited disease which involves goitre, increased free thyroid hormones with normal or elevated plasma TSH levels. The hormone resistance effect is more in keeping with the findings of this study. As

well as deafness, patients may present with mental retardation, short stature and delayed bone age.

Failure to Thrive (H-N-N)

The Failure to Thrive diagnostic group (FTT), showed a significantly high T_4, but did not show a significant result for T_3U or TSH, when compared to the control group. FTT showed varying significance upon stratification by puberty and sex. This is not a protein binding effect since T_3U was unaffected. It is difficult to ascertain why T_4 is significantly higher in the FTT group. However, the effect of a raised T_4 level is to increase basal metabolic rate (BMR) and energy consumption. Therefore, depletion of energy reserves by a raised T_4 may contribute to failure to thrive.

Slipped Epiphyses (H-N-N)

The Slipped Epiphyses diagnostic group (SE) showed a significantly high T_4, but there was no significant change in T_3U or TSH, when compared to the control group. There was varying significance upon stratification by puberty and sex. The small sample size for this group (total n = 9) must be taken into consideration in the interpretation of these results.

It was initially unclear as to why there should be any relationship between a raised T_4 level and slipped epiphyses. However, a study by Brenkel et al (1989) suggests a possible explanation. Fifteen patients with slipped capital femoral epiphyses were investigated, and no difference in skeletal or sexual maturity between the study groups, or any overt endocrine abnormality in the patients was found. However almost half the patients with slipped epiphyses were over the 90th weight percentile, suggesting that mechanical factors such as obesity are more important aetiologically than endocrine abnormalities. In the present study, it was found that T_4 was raised in obesity. If patients with slipped epiphyses are generally obese, then the SE group could be demonstrating similar findings to the OW group.

Turner's Syndrome (H-H-N)

In this study, the Turner's Syndrome (TS) diagnostic group showed a significant raised T_4, (especially post-puberty) and raised TSH results (especially pre-puberty) when compared to the whole control group (males and females). But T_3U was not significantly different from the control group in any of the stratified groups. Sex is a confounder in this group as Turner's Syndrome occurs only in females. T_4 in the TS diagnostic group was not significantly different from T_4 in control group females (Table 4.13). Therefore, sex is a potential confounder in this diagnostic group, although it must be noted that patients with Turner's Syndrome have only one X chromosome, so in a chromosomal sense, are not truly female.

Juvenile Chronic Arthritis (H-L-N)

In this study, the Juvenile Chronic Arthritis diagnostic group (JCA) showed a significantly high T_4 in females and in the pre-puberty groups. A significantly low TSH was noted only in the whole group, compared to the control group. T_3U was not significantly different to the control group in any of the stratified groups tested. These results should be interpreted with caution as the total group was comprised of only eight patients and this small sample size will affect the results. This is evidenced by the large confidence interval given with the median odds ratio result. Although the OR is 6.80, it is not significant as the confidence interval range includes the number 1. The quartile split could not be calculated. The results indicate central mechanisms are operating normally with TSH levels reduced in response to a raised T_4.

It appears likely that drugs used in therapy for juvenile chronic arthritis may alter T_4 metabolism. Herrmann, et al (1989) investigating the pathogenesis and clinical relevance of decreases of T_3 level in 63 patients with rheumatoid arthritis (59 of 63) and systemic lupus erythematosus (4 of 63) and found decreases and low normal values for the total T_3 in 33 of the 63 patients who were included in the study. The

remaining 30 patients exhibited a distinct reduction of total T_3 and free T_3, low normal total T_4, a moderate decrease of the basal and stimulated TSH, and only a very small restriction of the binding capacity of TBG. It is known that anti-rheumatic drugs, in particular glucocorticoids, may induce such a response *(Herrmann et al, 1989)*. Although patients on known drug therapy in this study were excluded from the analysis, most children with juvenile chronic arthritis would have been receiving drug therapy, even though it was not stated in the clinical notes.

Conclusions

In summary, it appears that of the diagnostic groups in the significantly low thyroxine category, Selected Diabetes is showing protein-binding as well as central or HPA effects; Thalassaemia is showing protein-binding effects; Growth Hormone Deficiency, Anorexia Nervosa, Acute Lymphoblastic Leukaemia and the Psychological Disorders diagnostic groups are showing direct thyroid gland effects; and Cystic Fibrosis is showing HPA effects.

Of the diagnostic groups in the significantly high thyroxine category, Obesity is showing protein-binding effects; Deafness, Failure to Thrive and Slipped Epiphyses are showing direct thyroid gland effects; Turner's Syndrome and Juvenile Chronic Arthritis are showing a HPA effects.

Many of these findings are novel and are pointers to new directions for future research in the relationship between thyroid hormone biochemistry and disease states, particularly with regard to Obesity, Anorexia Nervosa, Diabetes, Failure to Thrive and Cystic Fibrosis.

Having defined diagnostic groups where subtle differences occur in thyroxine levels compared to the control group, some limitations have been identified in the study. Patients with abnormal thyroid function tests have been excluded via primary and

secondary criteria. In future investigations, it is suggested that these excluded groups be included separately in the analysis and compared to the control group.

In inferring causality, it can be said that this study had good precision . Aspects of validity, i.e. confounding and measurement bias were well accounted for in this study, and it is thought that selection bias did not adversely affect the findings of this study. The degree of association in each case was substantial but not large (quartile odds ratio range 1.69 to 10.64) and most of these associations were supported by a dose response relationship in median and quartile split comparisons.

Care must be taken in the interpretation of these results. There are some strong biological hypotheses to support these findings. However, in a study of this type, a temporal relationship between exposure (thyroid function) and disease (diagnostic groups) cannot be defined. Further investigation would be required to confirm these findings. This would be best achieved by measuring free T_4 and TSH levels using the more sensitive and specific monoclonal antibody method currently available, on a larger sample size for the groups of interest.

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APPENDICES

A. *Ethics Submission*

B. *Diagnosis Codes*

C. *Conversion of combined diagnoses*

D. *Formation of diagnostic groups*

E. *Excluded neurological disorders*

F. *Frequency of diagnoses in patients aged less than 3 years of age*

G. *Frequency of diagnoses in patients aged 3-18 years of age*

APPLICATION FOR ETHICAL APPROVAL OF A PROJECT INVOLVING HUMANS

ALL QUESTIONS MUST BE ANSWERED

THIS APPLICATION MUST BE TYPEWRITTEN

*If this project includes any information of a commercial or patentable nature, this information should be sent separately and marked **"Confidential"**.*

1. **Project Title** (Working Title)

AN INVESTIGATION OF THYROXINE LEVELS IN A POPULATION OF SYDNEY CHILDREN INCLUDING NORMAL VERSUS DIAGNOSES OF DIABETES, LEUKAEMIA, OBESITY, ANOREXIA, LETHARGY AND TALLNESS.

2. **Name(s) Title(s) Department / Building Code / Location and Telephone Number(s) of Chief, Associate and Co-Investigators**

1. Anna Agnos, Student - Master of Community Health, Cumberland College of Health Sciences, University of Sydney. Telephone: 922 7688.

2. Dr. Kaye Brock, Senior Lecturer, Cumberland College of Health Sciences, University of Sydney, East Street, Lidcombe NSW 2141. Telephone: 646 6124.

3. Dr. John Earl, Developmental Biochemist, The Children's Hospital, Pyrmont Bridge Road, Camperdown NSW 2050. Telephone: 692 6280.

4. Dr. John Coakley, Head of Clinical Biochemistry, The Children's Hospital, Pyrmont Bridge Road, Camperdown NSW 2050. Telephone: 692 6633.

3. (A) **Proposed Date of Commencement of Project. You are reminded that Protocols should not commence without prior written approval from the Human Ethics Committee.**

November 1993

(B) **Proposed duration of project**

12 months

4. **Where will the procedures involving humans be undertaken?**

No contact with humans will be made as the project involves a detailed data analysis only. This analysis will be undertaken at The Children's Hospital,Camperdown.

Please Note: That the order of the "Yes" and "No" boxes are reversed in Questions: 10.3, 13, 17, 18, 19 (Part 2) and 24.

5. **The nature of this Research is best described as**

Therapeutic Research in which the experimental Intervention is expected to benefit the subject directly	[X] No	[ ] Yes
Therapeutic Research in which the experimental intervention is not expected to benefit the subject directly	[X] No	[ ] Yes
Clinical Trial. (Please indicate name of-pharmacologist involved in preparing the protocol below	[X] No	[ ] Yes

Human Physiology Research	[X] No	[ ] Yes
Behavioural Research	[X] No	[ ] Yes
Questionnaire only (Go directly to Question 14)	[X] No	[ ] Yes
Others (Please indicate nature of Research immediately below)	[ ] No	[X] Yes
Psychopathology	[X] No	[ ] Yes
Qualitative Evaluation Research	[X] No	[ ] Yes
Biomechanical Research	[X] No	[ ] Yes

Epidemiological analysis of previously collected data.

6. **Is there a requirement for violation of the integument of subjects (including drug absorption, needle stick, rectal probes, pharyngeal foreign bodies)?** ☒ No ☐ Yes

If you answered **YES** please state in what way the integument is planned to be violated, all the risks involved, and if possible with what incidence you expect these risks. (These risks must be included on the consent form).

7. **Is placental tissue used?** ☒ No ☐ Yes

8. **Is tissue planned for culture?** ☒ No ☐ Yes

9. **Are human embryos involved in the Research?** ☒ No ☐ Yes

10. **Is somatic gene cell therapy used?** ☒ No ☐ Yes

10.1 Is the disease being treated due to a defect in more than a single pair of genes? ☒ No ☐ Yes

10.2 Does the disease have an effective alternate treatment? ☒ No ☐ Yes

10.3 Does the diseases being treated have measurable index of response to therapy? ☐ Yes ☒ No

11. **Will radioactive substances be used?** ☒ No ☐ Yes

12. **Will the use of recombinant, DNA techniques, toxins, mutagens, teratogens or carcinogens be involved?** ☒ No ☐ Yes

13. **If a threat to health occurs to a subject are there sufficent facilities or contingencies available to deal with such problems?** N/A ☐ Yes ☐ No

14. Are the subjects: -

14.1	Children?	☐ No	☒ Yes
14.2	Elderly persons who may have legal capacity, but may be in a position where they are unable to give a free or comprehending consent?	☒ No	☐ Yes
14.3	Mentally ill?	☒ No	☐ Yes
14.4	Unconscious or critically ill patients?	☒ No	☐ Yes
14.5	Wards of state?	☒ No	☐ Yes
14.6	Prisoners?	☒ No	☐ Yes
14.7	Members of the armed services?	☒ No	☐ Yes
14.8	In a doctor-patient relationship?	☒ No	☐ Yes
14.9	In a health giver/health receiver (with respect to the researcher /subject) relationship?	☒ No	☐ Yes
14.10	In a teacher-student relationship	☒ No	☐ Yes
14.11	In an employer - employee relationship?	☒ No	☐ Yes
14.12	General public	☐ No	☒ Yes
14.13	Not Applicable	N/A ☐ No	☐ Yes

If you answered **Yes**, to 14.13 please give reasons

15. Is there a requirement for a department, school, faculty, or organisation to disclose information of personal details without written consent from the subject?

☐ No ☒ Yes

If you answered **YES** please state what these details are and why written consents not possible?

This project involves data analysis of laboratory tests collected over a number of years. All patient names will be assigned a unique code and these codes used in the analysis. Medical Records will not be accessed at any time.

16. Is there any possibility that personal details of a subject could be revealed to persons not directly connected with this project?

☒ No ☐ Yes

17. Will a written consent be obtained?

☐ Yes ☒ No

If you answered **NO** please give reasons (a consent form may be unnecessary for a questionnaire)

Please see Question 15.

18. Will a Subject Information Sheet be supplied (likely to be unnecessary for a questionnaire)?

☐ Yes ☒ No

If you answered **NO** please give reasons.

Not required - please see Question 15.

9. **Is the research targeting an Ethnic minority or Community group?** ☒ No ☐ Yes

If you answered **YES** what group are you targeting?

If you answered **YES** has this been done in consultation with a representative of this group? N/A ☐ Yes ☐ No

If you answered **YES** who have you consulted, and how do they represent this group?

10. **Is there psychological or physical stress placed on the subjects?** ☒ No ☐ Yes

If you answered **YES**, please state what this might be.

21. Is compensation planned for the subjects?

☒ No ☐ Yes

If you answered **YES**, is the compensation sufficient to act as an inducement to enrol?

N/A ☐ ☐ No Yes

If you answered **YES**, what is the amount and the justification for this?

22. Do the researchers expect to obtain any financial benefit from conducting this project?
(NB. this does not include grants)

☒ No ☐ Yes

If you answered **YES**, please explain.

23. Does recruitment of participants involve a direct personal approach from the researcher to the potential subject?

☒ No ☐ Yes

If you answered **YES**, is there any researcher or peer group pressure that might influence the potential subject to enrol.

N/A ☐ ☐ No Yes

If you answered **YES**, please explain reasons.

4. **Are the subjects <u>able</u> to withdraw from participating in the project at any time (this must be stated on the consent form or questionnaire)?**

☐ Yes ☒ No

(ie. subjects can withdraw at any time and are aware of this option)

If you answered **NO**, please state reasons.

Please see Question 15.

5. **Has this project been submitted to any other Ethics Committee?**

☒ No ☐ Yes

If you answered **YES**, please state which Committee?

6. **Has approval for this project been granted from any other Ethics Committee?**

☒ No ☐ Yes

If you answered **YES**, please attach a copy of the approval.

27. Brief outline proposed project and its importance (please do not exceed space provided as it will not be read)

(References to be included separately)

The thyroid hormones, and especially thyroxine (T4), have three principal effects on the body: (a) regulation of metabolism, (b) regulation of growth and development, and (c) regulation of the activity of the nervous system *(1)*. With respect to the regulation of metabolism, the thyroid hormones stimulate virtually all aspects of carbohydrate and lipid metabolism in most cells of the body and increase the rate of protein synthesis *(1)*.The thyroid hormones also help to regulate tissue growth and development, especially in children *(1)*.

Over 10 years data, on thyroid function tests have been collected by laboratory staff at the Children's Hospital, Camperdown in Sydney. Over this period, staff have noticed a possible trend in this data with respect to certain diseases.

The aim of this project is to review thyroxine and possibly free thyroxine index (FTI) and thyroid stimulating hormone (TSH) with sex and age in a number of different "normal" (control) and disease (case) groups via an extensive computer analysis of the data available. Variations in T4 within the normal range will be the focus of the research.

In the interests of maintaining patient anonymity, all patient data will be numerically coded for use during the analysis and in any subsequent publications. No use of Medical Records will be required at any stage of the project.

Control groups will be patients with the following diagnoses:
Short Stature for Investigation. Apart from the occasional case of hypo thyroidism which can be eliminated by abnormal T4 or TSH results, this is a relatively normal group.
Cystic Fibrosis. Growth problems are due to fat malabsorption rather than due to hormonal changes so this is group will also be used as a control group.

Cases include those with the following diagnoses:
Insulin-dependent Diabetes Mellitus. This type of diabetes (Type I), generally develops during childhood, the peak incidence being at puberty *(2)*. Insulin secretion by the pancreas is either substantially reduced or non-existent. As a result, changes in metabolism occur which lead to a variety of symptoms and can be fatal if left untreated *(2)*. It is thought that this group may have slightly lower T4 levels than normals.
Acute Lymphoblasic Leukaemia. This type of leukaemia is a malignant disorder of certain bone marrow cells of which the cause is unknown *(2)*. Typically the onset is acute or subacute in a previously healthy child, or less commonly, in an adult. Clinical symptoms include weakness, fatigue, infection and bleeding *(2)*. Leukaemia patients after their chemotherapy and radiotherapy are tested to see if they have

27. (continued)

damage to their pituitary gland, which regulates many of the body's hormones. *Obesity/Anorexia/Lethargy/Tallness.* It is not known whether minor differences in thyroid hormones play a role in these conditions.

Therefore it is anticipated that a comprehensive analysis of the data available will show the expected trends and ultimately lead to a better understanding of these important childhood diseases.

References

(1) Tortora, G.J. and Anagnostakos, N.P. (1987) *Principles of Anatomy and Physiology*, 5th edition, Harper & Row, New York.

(2) Rubin, E. and Farber, J.L. (eds.) (1988) *Pathology*, J.B. Lippincott Company, Philadelphia.

28. **Are there any further ethical considerations that you may wish to raise?**

☐ No ☒ Yes

If you answered **Yes**, please state what these considerations are.

As the raw data contains the names of patients and laboratory test results, each patient will be assigned a unique number to be used in subsequent data analysis. Once coded, the names and corresponding numbers will be destroyed, in the interests of preserving patient anonymity. Medical Records will not be accessed at any time.

29. **Checklist**

The following documents are attached (Please tick where applicable).

- ☐ Copy of Consent Form
- ☐ Copy of explanatory material for participants (subject information sheet)
- ☐ Evidence of permission to conduct research in locations not associated with the University of Sydney.
- ☐ Evidence of approval by another ethics committee
- ☐ References relevant to Question 27.
- ☐ Copy of Questionnaire (s) to be used in the research
- ☐ Copy of the statement from Medical/paramedical practitioner accepting responsibility for procedures.
- ☐ Copy of any ethical approval form requiring signature (eg. NH&MRC attachment I Certificate)

If approval is granted for this research, it will be done so, on the understanding that the enclosed information is a true record of my research.

Signature of Chief Investigator or Supervisor

Name: K. BROEK
(please print)

Signature Kaye Broek

Date 6/10/93

Signature of Associate Investigator

John Ecl

Date 14/10/93

Signature of Student

ANNA AGNOS -

Date 04/10/93

Signature of Dean of Faculty OR Head of Department OR Head of School

Name: PR C. RUSSELL
(please print)

Signature C Russell

Date 8/10/93

APPENDIX B

DIAGNOSIS CODES

Code	Meaning/Alternative
A	ALPHA-1 AT DEFICIENT
AA	ASPHYXIA/PERINATAL ASPHYXIA
AB	ABAGELLES SYNDROME
ABA	ADVANCED BONE AGE
ABN	ABNORMAL/ABNORMALITY
ABP	ABDOMINAL PAIN/ABDOMINAL DISCOMFORT OR BLOATING
AC	ACROMEGALY
ACS	ACIDOSIS
ACY	ANOVULATORY CYCLES
AD	ADDISONS DISEASE
ADR	HYPOADRENALISM
AF	ATRIAL FIBRILLATION
AG	AGGRESSION / EMOTIONAL LABILITY
AGD	ARGINASE DEFICIENCY
AI	ADRENAL INSUFFICIENCY
AIDS	ACQUIRED IMMUNE DEFICIENCY SYNDROME
ALB	LOW ALBUMIN
ALC	ALCOHOL ABUSE
ALL	ACUTE LYMPHOBLASTIC LEUKAEMIA
AM	AMENORRHOEA
AM1	PRIMARY AMENORRHOEA
AM2	SECONDARY AMENORRHOEA
AML	ACUTE MYELOBLASTIC LEUKAEMIA
AN	ANAEMIA - All types except Sickle Cell Anaemia
ANX	ANXIETY/AGITATION
AP	ALOPECIA (AREATO)/HAIR LOSS/FALLING HAIR
APN	APNOEA
ARR	CARDIAC ARRHYTHMIA/MURMUR
ART	ARTHRITIS/ARTHRALGIA/RHEUMATOID ARTHRITIS
AS	ASTHMA
AT	ATAXIA
AX	ANOREXIA NERVOSA/DEPRESSED APPETITE
AY	ARTHROGRYPOSIS
B	BLACKOUTS
B12	VITAMIN B12 DEFICIENCY
BA	BILIARY ATRESIA
BAD	BIPOLAR ACTIVE DISORDER
BC	BRADYCARDIA
BCH	BONE CHANGES/SKELETAL DYSPLASIA
BD	BEHAVIOURAL DISORDER/PROBLEM
BE	BONE PAIN
BH	BILATERAL HARRISON-SULKA DISEASE
BI	CONJUGATED BILIRUBIN
BL	BLIND/VISUAL DIFFICULTY
BO	BILATERAL PTOSIS
BR	BRONCHITIS/BRONCHIOLITIS
BS	SHORT BOWEL SYNDROME

BU	BULIMIA NERVOSA
C	CARDIAC DISEASE
CA	(MULTIPLE) CONGENITAL ABNORMALITY/MIDLINE DEFECTS
CAH	CONGENITAL ADRENAL HYPERPLASIA
CAN	CANDIDIDIASIS
CAR	CAROTENAEMIA
CAT	CATARACTS
CB	DECARBOXYLASE DEFICIENCY
CD	COELIAC DISEASE/"COELIAC"
CE	CHROMOSOME ABNORMALITY
CF	CYSTIC FIBROSIS
CH	CHOLESTASIS
CHD	CONGENITAL HEART DISEASE
CI	COLD INTOLERANCE/SENSITIVITY
CJ	CHOLESTATIC JAUNDICE
CM	CARDIOMYOPATHY
CN	CYSTINOSIS
CO	CRYPTORCHIDISM/UNDECENDED TESTES
COF	CONFUSION/DELIRIUM
COH	COHENS SYNDROME
COHD	CORONARY HEART DISEASE
CON	CONSTIPATION/INTESTINAL OBSTRUCTION
CQ	CHONDRODYSPLASIA
CR	CIRRHOSIS
CRF	CHRONIC RENAL FAILURE
CS	CUSHINGS SYNDROME/"CUSHINGOID"
CT	COARCTATION
CU	CYSTINURIA
CY	CYST/ARACHNOID CYST/BRACHIAL CYST
D	DIABETES
DBA	DELAYED OR RETARDED BONE/OSSEOUS AGE
DBD	DIAMOND BLACKFAN DEFICIENCY
DD	DEVELOPMENTAL DELAY/SLOW/MOTOR DELAY/DELAYED PROGRESS
DEAF	DEAFNESS/(CONGENITAL) HEARING LOSS OR DIFFICULTY
DEF	"DEFICIENCY"
DEP	DEPRESSION
DFE	DELAYED/ABSENT FEMORAL EPIPHYSES
DGD	DEGENERATIVE DISEASE/NEURODEGENERATIVE DISEASE
DH	DRY HAIR
DI	DIABETES INSIPIDUS/NEPHROGENIC DIABETES
DL	DENTITION LOSS
DM	DIABETES MELLITUS
DMY	DERMATOMYOSITIS
DO	DRY MOUTH
DP	DYSPEPSIA
DR	DIARRHOEA
DS	DOWN'S SYNDROME/TRISOMY 21
DT	DYSTONIA
DU	DUODENAL ULCER
DUS	DUMPING SYNDROME
DV	DEPRIVATION
DW	DWARFISM

DY	DYSMATURE
DYS	DYSMORPHIC/COARSE FEATURES/"DISMORPHIC"
DZ	DIZZINESS
EAT	EATING DISORDER/POOR FEEDING/FOOD INTOLERANCE
EB	EBSTEINS ANOMALY
EC	ECZEMA
ED	(POLY)EPIPHYSEAL DYSPLASIA
EN	ENEURESIS
EO	EXOPTHALMOS/PROMINENT EYES
ER	ENCOPORESIS
ES	EPISTAXIS
F	FEMALE
FAL	TERATOLOGY OF FALLOTS/"FALLOTS"
FDS	FOETAL DILANTIN SYNDROME
FH	FAMILY HISTORY
FL	FLOPPY BABY/FLOPPINESS
FSHD	FOLLICLE STIMULATING HORMONE DYSTROPHY
FTT	FAILURE TO THRIVE/POOR WEIGHT GAIN
FU	FLUSHING
FV	FEVER
GAIT	GAIT DISTURBANCE
GAL	GALACTOSAEMIA
GAST	GASTROSCHESIS
GAU	GAUCHERS DISEASE
GD	GROWTH DELAY, RETARDATION, FAILURE
GDIS	GROWTH DISORDER
GEN	AMBIGUOUS GENITATLIA
GHD	GROWTH HORMONE DEFICIENCY
GIG	GIGANTISM
GM	GYNAECOMASTIA
GP	G-6-PD DEFICIENCY
GR	GALACTORRHOEA
GRE	GREY HAIR/PREMATURE GREYING OF HAIR
GRS	GOULD REGRESSION SYNDROME
GS	GROWTH SPURT/RECENT GROWTH SPURT
H	HERNIA
HA	HYPERACTIVE/OVERACTIVE JITTERY
HB	CONGENITAL HYPERBILIRUBINAEMIA
HCAL	HYPOCALCAEMIA
HCH	HYPERCHOLESTEROLAEMIA
HCN	HOMOCYSTINURIA
HE	HAEMOPHILIA
HEP	HEPATITIS/CHRONIC ACTIVE HEPATITIS
HEP B	HEPATITIS B
HF	HYPOREFLEXIA
HG	HYPOGLYCAEMIA
HGO	HYPOGONADISM/GONADAL DYSGENESIS OR FAILURE
HH	HEMIHYPERTROPHY
HI	HIRSUTISM
HIN	HYPERINSULISM
HIP	HIRSCHSPRUNGS DISEASE
HK	HYPOPLASTIC KIDNEY

HLD	HYPERLIPIDAEMIA
HND	HYPERNATRAEMIC DEHYDRATION
HN	HYPOTONIA
HO	(POSTURAL) HYPOTENSION/LOW BLOOD PRESSURE
HOV	HYPOVENTILATION
HPAL	HYPOALUMINAEMIA
HPHR	HYPOPHOSPHATAEMIC RICKETS
HR	HYPERTRICHOSIS
HS	HEADACHES
HSM	HEPATOSPLENOMEGALY
HT	HYPERTENSION
HU	HURLERS DISEASE
HUS	HAEMOLYTIC URAEMIC SYNDROME
HV	HOARSE/HUSKY VOICE
HW	HISTIOCYTOSIS/HISTIOCYTOSIS X
HYN	HYDRONEPHROSIS
HYP	HYPOTHERMIA
IA	INCREASED APPETITE
IBS	IRRITABLE BOWEL DISEASE/ABNORMAL BOWEL MOTILITY
IC	ICTARUS
ID	AUTOIMMUNE DISORDER
IDDM	INSULIN DEPENDENT DIABETES MELLITUS
IF	IDDM NEPHROPATHY
IG	INCONTINENTIA PIGMENTIA
IH	HEAT INTOLERANCE
IHG	INCREASED HAIR GROWTH
IM	INFECTIOUS MONONUCLEOSIS
INF	VIRAL OR OTHER "INFECTION" (UNSPECIFIED)
IO	IRON OVERLOAD
IP	IRREGULAR PERIODS/MENSTRUAL IRREGULARITY
IR	IRRITABILITY
IS	INSOMNIA
J	JAUNDICE
JCA	JUVENILE CHRONIC ARTHRITIS
JRA	JUVENILE RHEUMATOID ARTHRITIS
LA	LYMPHADENOPATHY
LAC	LACTIC ACIDOSIS
LAF	LARGE OR WIDE ANTERIOR FONTANELLE/DELAYED CLOSURE OF FONTANEL
LET	LETHARGY/TIREDNESS/FATIGUE/SLEEPINESS
LF	LIVER FAILURE
LP	LIMB PAIN/LEG PAIN
LU	LUNG DISEASE
M	MALE
MA	MASTOPATHY
MAC	MACROCEPHALY/MEGALOCEPHALY/LARGE HEAD
MAL	MALAISE
MAP	MACROPHALLUS
MAR	MARFANS SYNDROME
MAS	McCUNE ALBRIGHES SYNDROME
MB	MALABSORPTION/LIPID OR STORAGE DISORDER
MD	MATURATION DELAY
MEN	MENORRHAGIA

MF	MULTI FOCAL THROMBI
MG	MYASTHENIA GRAVIS
MGL	MACROGLOSSIA/LARGE OR PROMINENT TONGUE
MIO	MICROPTHALMOS
MIP	MICROPHALLUS
MMA	METHYL MALONIC ACIDOSIS
MMC	MYELOMENINGOCOELE
MN	MYOTONIA
MNT	MALNUTRITION/INADEQUATE DIET
MO	MALROTATION
MOD	MATURITY ONSET DIABETES
MP	METABOLIC PROBLEM
MQ	MOOD DISTURBANCE
MT	METAPHYSICAL DISEASE
MU	MUSCLE PAIN
MW	MUSCLE WASTING
MX	PERSISTENT MOTTLING
MYO	MYOPATHY
N	NEPHROSIS/CONGENITAL NEPHROSIS
NA	NAUSEA
NAT	HYPONATRAEMIA
ND	NOONANS SYNDROME/DISEASE
NH	NEONATAL HEPATITIS
NIDDM	NON-INSULIN DEPENDENT DIABETES MELLITUS
NL	NARCOLEPSY
NP	NEUTROPAENIA
NYS	NYSTAGMUS
OC	OVARIAN/CERVICAL CYST
OE	OEDEMA
OFS	OPITZ FRIAR SYNDROME
OH	OPTIC (NERVE) HYPOPLASIA/OPTIC ATROPHY
OM	OLIGOMENORRHOEA
OP	OSTEOPOROSIS/JUVENILE OSTEOPOROSIS
OVE	OVARIAN ENLARGEMENT
OW	OVERWEIGHT/OBESE/PLUMP/INCREASED FAT
P	PALLOR/PALE
PA	PAPILLITIS
PALP	PALPITATIONS
PAT	GROWTH PATTERN
PBS	PRUNE BELLY SYNDROME
PC	PERICARDITIS
PD	PUBERTAL DELAY/PUBARCHE
PDA	PATIENT DUCTUS ARTERIOSIS
PDY	POLYDYPSIA/INCREASED DRINKING
PE	POLYENDOCRINOPATHY
PF	PUFFY FACE/EYES
PH	PREMATURE TITRACHE
PI	PSYCHOTIC ILLNESS/PSYCHOSIS
PLE	PROTEIN LOSING ENTEROPATHY
PM	POLYMYOSITIS/MYOSITIS
PMS	PREMENSTRUAL SYNDROME
PN	POLIOMYELITIS/"POLIO"

PNE	PNEUMONIA
PP	PRECOCIOUS PUBERTY OR DEVELOPMENT
PREM	PREMATURE
PS	PERTUSSIS
PT	PROPTOSIS
PU	POLYURIA
PUO	PYREXIA OF UNKNOWN ORIGIN
PV	PESCAVUS
PWG	POOR/SLOW WEIGHT GAIN
PWS	PRADER-WILLI SYNDROME
PY	PYREXIA
R	RUBELLA/CONGENITAL RUBELLA
RAY	RAYNAUDS PHENOMENON
RC	RENAL CALCULI
RCA	RED CELL APLASIA
RD	RENAL DISEASE/DYSPLASIA
RE	RESPIRATORY DISTRESS
RG	RAPID/ACCELERATED GROWTH
RN	RINGING IN HEAD
RP	RECTAL PROLAPSE
RSS	RUSSELL SILVER SYNDROME
RT	RETINOSIS PIGMENTOSA
RTA	RENAL TUBULAR ACIDOSIS
S	SWEATY/ MOIST PALMS/NIGHT SWEATS
SA	SICKLE CELL ANAEMIA
SAH	SUBARACHNOID HAEMORRHAGE
SAP	(INCREASED) SERUM ALKALINE PHOSPHATASE
SB	SPINA BIFIDA
SC	SCLEROSIS
SCH	SCHWACHMAN'S DISEASE
SD	SLOW DENTITION/DENTITION DELAY
SE	SLIPPED EPIPHYSES
SG	SLOW OR POOR GROWTH/DECREASED GROWTH RATE
SGA	SMALL FOR GESTATIONAL AGE
SI	STILLS DISEASE
SIADH	SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE
SJS	STEVEN JOHNSON SYNDROME
SK	SKIN DISORDER/SPIDER NAEVUS
SLE	SYSTEMIC LUPUS ERYTHEMATOSIS/"LUPUS"
SLOW	INACTIVE
SO	SOTOS SYNDROME
SPD	SPEECH DELAY
SPF	SMALL PITUITARY FOSSA
SQ	SQUINT
SS	SHORT STATURE/SMALL
SSG	SHORT SLOW GROWTH/SMALL SLOW GROWTH
ST	SPLENOCYTOSIS
SVT	SUPRAVENTRICULAR TACHYCARDIA
SYN	SYNCOPE/RECURRENT SYNCOPE
SW	SLOW TO WALK/DELAYED WALKING
T3U	TRIIODOTHYRONINE UPTAKE
T4	THYROXINE

TALL	TALL STATURE/TALLNESS
TC	TACCHYCARDIA/TACCHYARRYTHMIA
THAL	THALASSAEMIA
TL	TENDER LIVER
TN	THIN/SKINNY/UNDERWEIGHT/SLENDER/LOW WEIGHT
TPN	TOTAL PARENTERAL NUTRITION
TR	TREMOR
TS	TURNERS SYNDROME
TSH	THYROID STIMULATING HORMONE
U	SEX UNSPECIFIED
UC	ULCERATIVE COLITIS
UH	UMBILICAL HERNIA
UI	URINARY INCONTINENCE
URTI	UPPER RESPIRATORY TRACT INFECTION
UTI	URINARY TRACT INFECTION
V	VITILIGO
VB	VAGINAL BLEEDING/SPOTTING
VC	VOCAL CHORD PARALYSIS
VO	VOMITING
VR	VON RICK DISEASE
VSD	VENTRICULAR SEPTAL DEFECT
VUR	VESICO-URETERIC REFLUX/"REFLUX"
W	WASTING/GENERALISED WASTING
WD	WILLIAMS DISEASE
WG	WEIGHT GAIN
WK	WEAKNESS/POOR MUSCLE TONE
WL	WEIGHT LOSS/DECREASED WEIGHT VELOCITY
WP	WEIGHT PROBLEM

APPENDIX C

COMBINED DIAGNOSES CONVERSIONS*

Patients aged 3 - 18 years

A/LF	LF	DS/CHD	DS	LET/WL	WL
ALL/COF	ALL	DS/DEAF	DS	MAC/SPD	MAC
ALL/OW	ALL	DS/DEP	DS	MEN/IP	MEN
ALL/SG	ALL	DS/IP	DS	MEN/OW	OW
ALL/SS	ALL	DS/OW	DS	NA/LET/DEP	DEP
AML/SS	AML	DS/SG	DS	ND/SS	ND
AML/WG	AML	DS/SS	DS	OW/?CS	OW
AN/SLOW	AN	DU/OW	DU	OW/?PP	OW
AN/SS	AN	DZ/V	V	OW/ABP	OW
AN/WL	AN	EB/SS	EB	OW/ANX	OW
ANX/TR	ANX	EN/?UTI	EN	OW/CAT	OW
ARR/SLOW	ARR	FTT/ABP	FTT	OW/CON	OW
ART/FV	ART	FTT/CI	FTT	OW/EAT	OW
AS/TC	AS	FTT/SS	FTT	OW/GM	OW
AX/HN	AX	FTT/VO	FTT	OW/HI	OW
BP/SS	BP	FTT/W	FTT	OW/HLD	OW
C/FH	C	GAU/SS	GAU	OW/HS	OW
CAH/PP	CAH	GS/CAH	CAH	OW/HT/SLOW	OW
CAH/SG	CAH	HA/TN	TN	OW/IP	OW
CAH/SS	CAH	HEMPAS/IO	IO	OW/PN	OW
CAH/WG	CAH	HEP/WL	HEP	OW/SLOW	OW
CD/OW	CD	HI/OW	OW	OW/SS	SS
CD/WL	CD	HS/DZ	HS	P/SS	SS
CF/IDDM	CF	HS/MAL	HS	PALE/SS	SS
CF/MNT	CF	HS/WL	WL	PDY/PU	PU
CF/SS	CF	HW/?DI	HW	PKU/SS	PKU
CHD/HF	CHD	IDDM/?CD	IDDM	PP/OW	PP
CHD/SS	CHD	IDDM/CAR	IDDM	PP/SG	PP
CHD/TC	CHD	IDDM/DEP	IDDM	PP/TALL	PP
CON/BC	CON	IDDM/DR	IDDM	PWG/HA	PWG
CON/LET	CON	IDDM/GD	IDDM	PWS/SS	PWS
CON/OW	OW	IDDM/HT	IDDM	R/OW	OW
CON/SS	SS	IDDM/LET	IDDM	RD/SS	RD
CRF/CI	CRF	IDDM/OE	IDDM	SE/OW	SE
CU/SS	CU	IDDM/SG	IDDM	SG/CAH	CAH
D/AP	D	IDDM/SS	IDDM	SG/IDDM	IDDM
D/GD	D	IDDM/TL	IDDM	SG/OW	OW
D/SG	D	IDDM/WL	IDDM	SLE/PD	SLE
D/SS	D	JCA/?PAT	JCA	SLE/SS	SLE
D/SS/OW	D	JCA/SS	JCA	SLOW/LET/WG	WG
D/WL	D	LA/SS	SS	SLOW/OW/HN	OW
DD/DEAF	DD	LEAN/HA	HA	SLOW/SS	SS
DD/HN	DD	LET/?AN	LET	SS/?DV	SS
DD/P	DD	LET/COLD	LET	SS/ABP	SS
DD/SS	DD	LET/DZ	LET	SS/AML	AML
DD/SS/?PWS	DD	LET/HPHR	HPHR	SS/ANX	SS
DD/WG	DD	LET/MGL	MGL	SS/ART	ART
DEAF/DD	DD	LET/P	LET	SS/AS	AS
DM/GD	DM	LET/SPD	SPD	SS/BCH	BCH
DM/SG	DM	LET/WG	WG	SS/COLD/FTT	FTT
DM/SS	DM	LET/WK	LET	SS/CON	SS

* for diagnosis codes see Appendix B.

SS/D	D
SS/DBA	SS
SS/DD	DD
SS/DR	SS
SS/DYS	DYS
SS/EAT	EAT
SS/EC	SS
SS/EN	SS
SS/EP	EP
SS/FTT	FTT
SS/GD	SS
SS/HT	HT
SS/HV	SS
SS/IDDM	IDDM
SS/INF	INF
SS/LET	SS
SS/LU	LU
SS/MB	MB
SS/MD	SS
SS/MYO	MYO
SS/ND	ND
SS/OP	OP
SS/PD	PD
SS/PP	PP
SS/SLOW	SS
SS/SLOW/CON	SS
SS/THAL	THAL
SS/TN	SS
SS/TS	TS
TALL/?AC	TALL
TALL/?DBA	TALL
TALL/ABA	TALL
TALL/CLUMSY	TALL
TALL/HA	TALL
TC/RD	RD
THAL/AP	THAL
TN/S	TN
TR/ANX	ANX
TR/AT	AT
TS/SG	TS
TS/SS	TS
UTI/LET/AP	UTI
UTI/WG/PDY	UTI
VO/ABP	VO
VO/SS	VO
VO/WL	VO
VSD/SS	VSD
WG/LET	WG
WG/OC	OC
WK/AX	AX
WL/AX	AX
WL/LET	WL
WL/P	WL
WL/S	WL

Secondary

SS/OW	OW
OW/DD	OW
OW/PP	OW
OW/PD	OW
OW/DEP	OW
OW/MIP	OW

Patients aged less than 3 years

ALL/CON	ALL
APN/DD	DD
CA/EAT/PWG	CA
CAN/SAP	CAN
CF/HYP/TPN	CF
CON/DD	DD
CON/FTT	FTT
CON/WL	WL
DD/CON	DD
DD/FL	DD
DD/HN	DD
DD/MYO	DD
DD/SD	DD
DD/STRIDOR	DD
DEAF/SS	SS
DS/CON	DS
DS/FTT	DS
DS/HN	DS
DS/SS	DS
FTT/CON	FTT
FTT/HA	FTT
FTT/HV	FTT
FTT/HYP	FTT
FTT/LAF	FTT
FTT/LET	FTT
FTT/MX	FTT
FTT/P	FTT
FTT/SLOW	FTT
FTT/SMALL	FTT
FTT/SS	FTT
GD/UH	GD
HG/CON	HG
HN/IR	HN
HYP/INF	INF
J/BA	BA
J/CON	J
J/DS	DS
J/EAT	J
J/MIP	MIP
J/PREM	PREM
LAF/FTT	FTT
LET/WL	WL
MGL/DD	DD
ND/SS	SS
NYS/DD	DD
OW/EAT	OW
OW/P	OW
PDA/SS	PDA
PREM/DR	PREM
PREM/FTT	PREM
PREM/J	PREM
PS/UH	PS
PUO/S	PUO
R/SS	R
RSS/SS	RSS
SB/FTT	SB
SB/OW/HN	SB
SLOW/DD	DD
SLOW/WG	WG
SQ/DD	DD
SS/AN	AN
SS/BCH	BCH
SS/CON	SS
SS/DBA	SS
SS/DD	DD
SS/DD/HO	DD
SS/FTT	FTT
SS/HCAL	HCAL
SS/SCH	SCH
SS/SLOW	SS
TALL/HA	TALL
THAL/FTT	THAL
UH/EAT	EAT
UTI/FTT	UTI
VO/FTT	FTT
VSD/FTT	VSD
WG/UH	WG
WL/CON	WL

APPENDIX D

Formation of Diagnostic Groups*
Number in patients aged 3-11 years

1 SHORT STATURE NON-ENDOCRINE	n	2 IDDM	n	3 OBESITY	n
		2A		**3A**	
SS	1114	IDDM	395	OW	174
SG	15	D	34		
SSG	13	DM	32	**3B**	
GD	11	DI	3	WG	8
MD	2	MOD	1		
DW	0	NIDDM	0		
GDIS	0				
		2B			
		IDDM	395		
		D	34		
		DM	32		
		MOD	1		
		NIDDM	0		

* for diagnosis codes see Appendix B.

4 MALNUTRITION	n
4A	
FTT	46
4B	
CF	32
4C	
WL	31
4D	
AX	17
4E	
EAT	6
4F	
TN	5
4G	
BS	2
4H	
CD	2
4I	
MB	2
4J	
PWG	2
4K	
MNT	1
4L	
PLE	0
4M	
SCH	0
4N	
SR	0
4O	
UC	0
4P	
W	0

5 TALL STATURE	n
5A	
TALL	63
5B	
TALL	63
RG	4
(MAR)	3
GIG	3
GS	3
(SO)	1

6 HEART DISEASE	n
6A	
TC	12
6B	
TC	12
ARR	3
AF	2
PALP	2
BC	0
6C	
TC	12
CHD	4
ARR	3
AF	2
PALP	2
CT	1
EB	1
BC	0
FAL	0

7 PUBERTAL DISORDERS	n
7A	
PP	59
7B	
PD	39

8 NEUROLOGICAL DISORDERS	n
DD	47

9 CONNECTIVE TISSUE DISEASE	n
9A	
JCA	8
9B	
JCA	8
MG	4
SLE	3
ID	2
DMY	1
JRA	1
SJS	1
RAY	0
SI	0
9C	
ART	5
9D	
JCA	8
ART	5
9E	
MG	4
SLE	3
ID	2
DMY	1
JRA	1
SJS	1
RAY	0
SI	0

10 BLOOD DISORDERS	n
10A	
THAL	52
10B	
AN	7
10C	
AN	7
SA	2
DBD	1
GP	1
RCA	1
10D	
HT	4

11 PSYCHOLOGICAL DISORDERS	n
11A	
ANX	4
11B	
BD	3
11C	
HA	4
DEP	3
AG	1
BAD	1
COF	1
PI	1
DV	0
11D	
ANX	4
BD	3
HA	4
DEP	3
AG	1
BAD	1
COF	1
PI	1
DV	0

12 MENSTRUAL DISORDERS	n
12A	
VB	5
MEN	4
OM	4
IP	2
ACY	1
PMS	1
12B	
AM	3
AM1	6
AM2	8

13 NON-THYROIDAL ENDOCRINE DISORDERS	n
13A	
GHD	50
13B	
CAH	19
13C	
GHD	50
CAH	19
AD	5
CS	5
AI	1
PE	1
AC	0
ADR	0
HIN	0
13D	
CAH	19
AD	5
CS	5
AI	1
PE	1
AC	0
ADR	0
HIN	0

14 GENETIC DISEASES	n
14A	
TS	47
14B	
DS	30
14C	
ND	10
14D	
PWS	8
14E	
CN	6
14F	
XXY	1

15 LEUKAEMIAS	n
15A	
ALL	20
15B	
AML	5

16 LETHARGY	n	17 HAIR DISORDERS	n	18 DEAFNESS	n	19 CON	n
16A		**17A**		DEAF	25	**19A**	
LET	45	AP	21			CON	10
16B		**17B**				**19B**	
WK	5	HI	12			ABP	9
16C						**19C**	
MAL	3					CON	10
						ABP	9
16D							
LET	45					**19D**	
WK	5					DR	1
MAL	3						
						19E	
						CON	10
						ABP	9
						DR	1

20 BONE DISORDERS	n	21 MALE DEVELOPMENT	n	22 TREMOR	n	23 RENAL DISEASE	n
20A		**21A**		**22A**		CN	6
DBA	6	GM	10	TR	8	CRF	3
						PBS	2
20B		**21B**		**22B**		RD	2
SE	9	HGO	6	S	7	UTI	2
						IF	1
				22C		GL	0
				TR/S	1	HK	0
						HUS	0
				22D		HYN	0
				TR	8	N	0
				S	7	NS	0
						RC	0
						RTA	0
						VUR	0

24 NAUSEA/ VOMITING	n	25 HEAD	n	26 RESPIRATORY DISORDERS	n	27 MISCELLANEOUS GROUP	n
						V	6
24A		**25A**		**26**		OP	5
NA	3	SYN	6	AS	6	SSSFD	5
						EN	4
24B		**25B**		**(26B)**		HPHR	4
VO	5	HS	6	AA	0	EO	3
						HCAL	3
24C		**25C**				INF	3
NA	3	DZ	0			MYO	3
VO	5					OH	3
						PDY	3
						PU	3
						SB	3
						ALL/HEP B	2
						BN	2
						CAT	2
						CU	2
						ED	2
						GAU	2
						GRE	2
						HO	2
						HR	2
						HV	2
						IH	2
						LP	2
						PM	2
						R	2
						SPD	2
						SS/FSHD	2
						WL/VO	2
						ALC	1
						AN/CAN	1
						AT	1
						AZ	1
						B	1

BCH	1	ES/ABP	1	LAC	1	SFR	1
BE	1	FDS	1	LEG SP	1	SG/SLOW	1
BE/WL	1	FH/COHD	1	LET/HS	1	SK	1
BL/DEAF	1	FTT/DD	1	LU	1	SLOW	1
BOILS	1	FTT/SS/HEP B	1	MA	1	SLOW/DH	1
BP	1	FU/HS	1	MAC	1	SMALL	1
BU	1	GAIT	1	MBD	1	SS/OW/HT	1
C	1	GAL	1	MGL	1	SS/WG	1
C	1	GAL	1	MIO	1	SSF/DD	1
CA	1	GD	1	MIP	1	ST/PWG	1
CAN	1	GM/SS	1	MMA	1	SVT	1
CE	1	GR	1	MMC	1	TAA/ABA	1
CF/CR	1	GR	1	MU/MQ	1	TALL/OW	1
CHD/DEAF	1	GRS/GD	1	MW	1	TC/EO	1
CI	1	HCN	1	NL	1	TC/LET	1
CM	1	HE	1	NP	1	UI	1
CO	1	HERNIA	1	OC	1	URTI	1
COH	1	HG	1	PA	1	VC PALSY	1
CY	1	HGH DEF	1	PALE/LET	1	VC-OE	1
D/UC	1	HOV	1	PC	1	VDRR	1
DCC	1	HR	1	PD/DD	1	VR	1
DD/AN	1	HS/?PDY	1	PF	1	VSD	1
DEAF/SLOW	1	HS/LET	1	PH	1	WL/?AX	1
DEP/AS	1	HSM	1	PKU	1	WL/AM	1
DGD	1	HU	1	PR/FTT	1	WL/DR	1
DH	1	HW	1	PT	1	WP	1
DI/GHD	1	IA	1	PUO	1		
DL	1	ID/HEP	1	PV	1		
DO	1	IDDM/CD	1	QUIET/CON	1		
DP	1	IHG	1	RN	1		
DT	1	IM	1	RT	1		
DU	1	IO	1	SB/SS	1		
DYS	1	IP/EO	1	SC	1		
DYS/?V	1	IS	1	SDS	1		
ER	1	JVA	1	SFE?/SFK	1		

APPENDIX E

Secondary Exclusion Criteria - Neurological Disorders excluded

Primary/Secondary Diagnosis Code*	Frequency	Primary/Secondary Diagnosis Code*	Frequency
MR	44	EP/MR	1
SS/MR	14	FTT/EP	1
SEI	13	HN/MR	1
HC	7	HPC	1
CNSD	4	MAC/MR	1
CP	4	MIC/DD	1
EP	4	MNG/DD	1
CC	3	MR/HGO	1
FTT/SEI	3	MR/OW	1
MIC/MR	3	MR/SD	1
QU	3	MR/SS	1
SOD	3	OW/MR	1
DD/MIC	2	PD/MR	1
DD/MR	2	PP/MR	1
GB	2	PP/SEI	1
MIC	2	PREM/MR	1
MR/AT	2	PWG/MR	1
SP	2	QU/SEI	1
SS/SEI	2	RC/AN/HN/MR	1
TSC	2	SEI/CP	1
ADD	1	SEI/DYS	1
AE	1	SS/DEAF/MR	1
CAR/SEI	1	SS/HC	1
CHD/HC	1	SS/MIC	1
CHOREA	1	SS/MR/PT	1
CP/SS	1	SS/OW/MR	1
DA	1	V/MR	1
DEAF/HP	1	WL/EP/MR	1
DI/MIC	1		
EP	1		
EP/CNSD	1	**Total**	**160**

* for diagnosis codes see Appendix B.

APPENDIX F

Frequency of Diagnoses in patients aged less than 3 years of age

Diagnosis*	Frequency	Diagnosis	Frequency	Diagnosis	Frequency
FTT	198	BC	2	CH	1
J	167	CAR	2	CJ	1
SS	121	CHD	2	CON/RP	1
DD	87	CO	2	CON/SLOW	1
DEAF	37	CON/LET	2	CON/VO	1
CON	33	DD/SS	2	CQ	1
HN	21	DFE	2	CRF	1
DS	16	DH	2	CY	1
IDDM	15	DS/HIP	2	DD/DYS	1
SG	12	FTT/MB	2	DD/MAC	1
PP	10	GAL	2	DD/MGL	1
PREM	10	HGO	2	DD/PP	1
FL	9	HPHR	2	DEAF/DD	1
HYP	9	HT	2	DM	1
MGL	9	IBS	2	DS/CHD	1
LAF	8	MB	2	DW	1
DBA	7	OE	2	EAT/LET/DR	1
AN	6	PR	2	EO	1
GD	6	PUO	2	EO/RE	1
MIP	6	SB	2	FTT/AN	1
SW	6	THAL	2	FTT/CA	1
CA	5	WG	2	FTT/INF	1
DYS	5	WK	2	FTT/IR/RE	1
EAT	5	ADR	1	FTT/J	1
FTT/DD	5	AN/FTT	1	FTT/PS	1
HA	5	AN/J	1	FTT/VO	1
HG	5	APN/BC	1	GEN	1
OW	5	APN/FTT	1	GHD	1
DI	4	AS/DD	1	HH	1
AP	3	AT	1	HIN/GHD	1
CN	3	AY	1	HND	1
D	3	BA	1	HR	1
DR	3	BCH	1	HSM	1
HCAL	3	BH	1	HUS	1
LET	3	BI	1	HYN	1
OH	3	BR	1	IC	1
TALL	3	BR/VUR	1	INF	1
TS	3	CAN	1	IR	1
WL	3	CB	1	J/AN	1
ALL	2	CCHD	1	KY	1
AX	2	CF	1	LET/DR	1

*for diagnosis codes see Appendix B.

Diagnosis	Frequency	Diagnosis	Frequency
LET/DR/VO	1	SS/AS/EC	1
LET/EAT	1	SS/DEAF	1
LF	1	SS/OW	1
MAC	1	SSG	1
MAP	1	SSSFD	1
MG	1	SVT	1
MGL/COARSE/LET	1	TC	1
MGL/EAT	1	TN/HV	1
MGL/LET	1	UTI	1
MGL/SD	1	V	1
MN	1	VC	1
MNT	1	VSD	1
MO	1	VUR	1
MYO	1		
NH	1		
NP	1		
OC	1		
OVE	1		
PAT	1		
PDA	1		
PF	1		
PLE	1		
PS	1		
PS/ALB	1		
PWG	1		
PWS	1		
PY/ACS	1		
R	1		
RAY	1		
RD	1		
RSS	1		
RTA	1		
SAH	1		
SCH	1		
SD	1		
SI	1		
SIADH	1		
SLOW/HN	1		
SMALL	1		
SOG	1		
SPF	1		

APPENDIX G

Frequency of Diagnoses encountered in patients aged 3 - 18 years

Diagnosis*	Frequency	Diagnosis	Frequency	Diagnosis	Frequency
SS	1114	EAT	6	PDY	3
IDDM	395	HGO	6	PU	3
OW	169	HS	6	SB	3
TALL	63	SYN	6	SLE	3
PP	61	V	6	AF	2
THAL	52	AD	5	BN	2
GHD	50	AML	5	BS	2
DD	48	ART	5	C	2
TS	47	CS	5	CAT	2
FTT	46	HCH	5	CD	2
LET	45	OP	5	CU	2
PD	41	SSSFD	5	ED	2
D	34	TN	5	GAL	2
CF	32	VB	5	GAU	2
DM	32	VO	5	GR	2
WL	31	WK	5	GRE	2
DS	30	ANX	4	HCN	2
DEAF	25	CHD	4	HO	2
AP	21	EN	4	HR	2
ALL	20	HA	4	HV	2
CAH	19	HPHR	4	ID	2
AX	17	HT	4	IH	2
SG	15	MEN	4	IP	2
SSG	13	MG	4	LP	2
HI	12	OM	4	MB	2
TC	12	RG	4	MD	2
GD	11	AM	3	PALP	2
CON	10	ARR	3	PBS	2
GM	10	BD	3	PM	2
ND	10	CRF	3	PWG	2
ABP	9	DEP	3	R	2
SE	9	DI	3	RD	2
AM2	8	EO	3	SA	2
JCA	8	GIG	3	SPD	2
PWS	8	GS	3	SS/FSHD	2
TR	8	HCAL	3	UTI	2
WG	8	INF	3	WL/VO	2
AN	7	MAL	3	AB	1
S	7	MAR	3	ACY	1
AM1	6	MYO	3	AG	1
AS	6	NA	3	AI	1
CN	6	OH	3	ALC	1
DBA	6	PB	3	ALL/HEP B	1

*for diagnosis codes see Appendix B.

Diagnosis	Frequency	Diagnosis	Frequency	Diagnosis	Frequency
AN/CAN	1	ER	1	MMA	1
AT	1	ES/ABP	1	MMC	1
AZ	1	FDS	1	MNT	1
B	1	FH/COHD	1	MOD	1
BAD	1	FTT/DD	1	MU/MQ	1
BCH	1	FTT/SS/HEP B	1	MW	1
BE	1	FU/HS	1	NL	1
BE/WL	1	GAIT	1	NP	1
BL/DEAF	1	GM/SS	1	OC	1
BOILS	1	GP	1	OW/DEP	1
BP	1	GRS/GD	1	OW/MIP	1
BU	1	HE	1	OW/PD	2
CA	1	HEP	1	PA	1
CAN	1	HERNIA	1	PALE/LET	1
CE	1	HG	1	PB/SS	1
CF/CR	1	HGH DEF	1	PC	1
CHD/DEAF	1	HOV	1	PD/DD	1
CI	1	HS/LET	1	PE	1
CM	1	HSM	1	PF	1
CO	1	HU	1	PH	1
COF	1	HW	1	PI	1
COH	1	IA	1	PKU	1
CT	1	ID/HEP	1	PMS	1
CY	1	IDDM/CD	1	PR/FTT	1
D/UC	1	IF	1	PT	1
DBD	1	IHG	1	PUO	1
DCC	1	IM	1	PV	1
DD/AN	1	IO	1	QUIET/CON	1
DEAF/SLOW	1	IP/EO	1	RCA	1
DEP/AS	1	IS	1	RN	1
DGD	1	JRA	1	RT	1
DH	1	JVA	1	SB/SS	1
DI/GHD	1	LAC	1	SC	1
DL	1	LEG SP	1	SDS	1
DMY	1	LET/HS	1	SFR	1
DO	1	LF	1	SG/SLOW	1
DP	1	LU	1	SJS	1
DR	1	MA	1	SK	1
DT	1	MAC	1	SLOW	1
DU	1	MBD	1	SLOW/DH	1
DYS	1	MGL	1	SMALL	1
DYS/?V	1	MIO	1	SO	1
EB	1	MIP	1	SS/OW/HT	1

Diagnosis	Frequency
SS/WG	1
SSF/DD	1
ST/PWG	1
SVT	1
TAA/ABA	1
TALL/OW	1
TC/EO	1
TC/LET	1
TR/S	1
UI	1
URTI	1
VC PALSY	1
VC-OE	1
VDRR	1
VR	1
VSD	1
WL/AM	1
WL/DR	1
WP	1
XXY	1