From Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

HYPERTHYROIDISM: INCIDENCE AND LONG TERM QUALITY-OF-LIFE

Mirna Abraham Nordling, MD

Stockholm 2008
To the memory of my father
ABSTRACT

Hyperthyroidism is a common disorder which in general affects approximately 2% of women and 0.2% of men. There are three main types of hyperthyroidism, caused by increased thyroid hormone production: Graves’ disease, toxic multinodular goitre and solitary toxic adenoma. Three main treatment modalities are common for Graves’ hyperthyroidism: surgery, radioiodine, or antithyroid drugs. The aim of this thesis was to investigate the incidence of hyperthyroidism and the possible influence of the choice of treatment for Graves’ hyperthyroidism on health-related aspects of quality of life after 14-21 years, furthermore, to study whether patients with a history of hyperthyroidism, especially Graves’ disease, have an increased risk of committing suicide later in life.

In the first study, the total, age-specific incidence and the incidence of subgroups of hyperthyroidism in the county of Stockholm were determined during the years 2003-2005. They were identified by the clinical status, the thyroid hormone and antibody levels and in some cases by thyroid scintigraphy. Eight specialised units/hospitals in the county of Stockholm participated in the registration. During this period 1431 new well defined cases of hyperthyroidism on adults ≥ 18 years of age were diagnosed. The total annual incidence was found to be 32.7/100 000. The annual incidence of Graves’ disease was 24.5/100 000, of toxic nodular goitre 3.3/100 000 and of solitary toxic adenoma 4.9/100 000.

In the second and third studies we focused on long-term differences in health-related aspects of quality of life of patients who had been randomised in 1983-1990 to treatment with antithyroid drugs, surgery, or radioiodine for Graves’ hyperthyroidism. The treatment groups were compared with an age-and sex-matched Swedish reference population and with one another. We also addressed the question whether the quality of life was influenced by the current thyroidal hormonal status or the level of thyroxine (T4) substitution. Two quality of life questionnaires (36-item Short Form Health Status Survey (SF-36) and Quality of Life 2004 (QoL2004)) were answered by the patients and hormonal status was recorded. The results showed a lower SF-36 score on mental aspects of quality of life (p<0.05) and vitality (p<0.05) compared with a reference Swedish population. There were no differences in quality of life score between the three modes of treatment for Graves’ hyperthyroidism. We also found that the results obtained with SF-36 were not related to the current serum levels of thyroid hormones, as subjects with suppressed S-TSH reported QoL scores above as well as below the average score for the general reference population in both physical component summary and mental component summary.

In the fourth study, the risk of suicide among patients with a history of hyperthyroidism was investigated, since a pilot study had indicated an elevated suicide rate among patients previously treated for Graves’ hyperthyroidism. A comprehensive retrospective cohort study was therefore performed. The cohort included 43 633 patients who had been treated with radioiodine or surgically for hyperthyroidism in the years 1950-2005. The number of observed deaths in the cohort was compared with the expected, based on the suicide death rate in the age-, gender- and calendar period-matched general Swedish population, yielding standardised mortality ratios (SMR). The total SMR was 1.24 (95% CI, 1.04-1.47). The overall SMR among men and women with a history of Graves’ disease was 1.35 (95% CI, 1.07 - 1.66). A likely increase in risk of suicide among patients with a history of hyperthyroidism was observed.
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 LIST OF ARTICLES</td>
<td>2</td>
</tr>
<tr>
<td>2 LIST OF ABBREVIATIONS</td>
<td>2</td>
</tr>
<tr>
<td>3 INTRODUCTION</td>
<td>3</td>
</tr>
<tr>
<td>3.1 Anatomy</td>
<td>3</td>
</tr>
<tr>
<td>3.2 Embryology</td>
<td>3</td>
</tr>
<tr>
<td>3.3 Physiology</td>
<td>4</td>
</tr>
<tr>
<td>3.4 Epidemiology of hyperthyroidism</td>
<td>7</td>
</tr>
<tr>
<td>3.5 Subgroups of hyperthyroidism</td>
<td>7</td>
</tr>
<tr>
<td>3.5.1 Graves’ disease</td>
<td>9</td>
</tr>
<tr>
<td>3.5.2 Toxic multinodular goitre</td>
<td>9</td>
</tr>
<tr>
<td>3.5.3 Solitary toxic adenoma</td>
<td>10</td>
</tr>
<tr>
<td>3.6 Symptoms and Diagnosis of hyperthyroidism</td>
<td>11</td>
</tr>
<tr>
<td>3.7 Treatment of hyperthyroidism</td>
<td>13</td>
</tr>
<tr>
<td>3.7.1 Antithyroid drug</td>
<td>13</td>
</tr>
<tr>
<td>3.7.2 Radioiodine</td>
<td>14</td>
</tr>
<tr>
<td>3.7.3 Surgery</td>
<td>15</td>
</tr>
<tr>
<td>3.8 Quality of life and Suicide</td>
<td>18</td>
</tr>
<tr>
<td>4 AIMS OF THE THESIS</td>
<td>21</td>
</tr>
<tr>
<td>5 PATIENTS AND METHODS</td>
<td>23</td>
</tr>
<tr>
<td>5.1 Paper I</td>
<td>23</td>
</tr>
<tr>
<td>5.2 Papers II and III</td>
<td>25</td>
</tr>
<tr>
<td>5.3 Paper IV</td>
<td>28</td>
</tr>
<tr>
<td>6 RESULTS</td>
<td>32</td>
</tr>
<tr>
<td>6.1 Paper I</td>
<td>32</td>
</tr>
<tr>
<td>6.2 Paper II</td>
<td>34</td>
</tr>
<tr>
<td>6.3 Paper III</td>
<td>37</td>
</tr>
<tr>
<td>6.4 Paper IV</td>
<td>39</td>
</tr>
<tr>
<td>7 DISCUSSION</td>
<td>41</td>
</tr>
<tr>
<td>8 CONCLUSIONS</td>
<td>49</td>
</tr>
<tr>
<td>9 SUMMARY IN SWEDISH</td>
<td>50</td>
</tr>
<tr>
<td>10 ACKNOWLEDGEMENTS</td>
<td>52</td>
</tr>
<tr>
<td>11 REFERENCES</td>
<td>54</td>
</tr>
<tr>
<td>12 APPENDIX</td>
<td>64</td>
</tr>
<tr>
<td>12.1 The Incidence form</td>
<td>64</td>
</tr>
<tr>
<td>12.2 QoL-2004</td>
<td>64</td>
</tr>
<tr>
<td>12.3 SF-36</td>
<td>64</td>
</tr>
</tbody>
</table>
1 LIST OF ARTICLES


*Eur J Endocrinol.* Accepted


*Thyroid. 2005 Nov; 15(11):1279-1286*


*Eur J Endocrinol. 2007 Feb; 156(2): 173-179*


*JAMA,* Submitted
RELATED ARTICLES NOT INCLUDED IN THE THESIS


*Eur J Endocrinol. 2008 Jan; 158(1): 69-75*


*BMC Endocrine Disorders, Submitted*
LIST OF ABBREVIATIONS

2 LIST OF ABBREVIATIONS

GD Graves’ disease
TMNG Toxic multinodular goitre
STA Solitary toxic adenoma
TAO Thyroid associated ophthalmopathy
ATD Antithyroid drugs
\(^{131}\)I Radioiodine
HRQoL Health-related Quality of Life
QoL Quality of Life
SF-36 Short Form-36 Health Survey
QoL-2004 Quality of Life 2004 questionnaire
MCR Mental Component Summary
PCR Physical Component Summary
ICD International Classification of Diseases
SMR Standardised Mortality Ratio
T\(_3\) Triiodothyronine
T\(_4\) Thyroxine
TRH Thyrotropin releasing hormone
TSH Thyroid-Stimulating Hormone, Thyrotropin
TSHR Thyrotropin receptor
TRAb Thyrotropin receptor antibodies
Tg Thyroglobulin
TPO Thyroperoxidase
NIS \(\text{NA}^+$/I symmetric transporter\)
3 INTRODUCTION

THE THYROID GLAND

3.1 ANATOMY

The thyroid is an endocrine gland located on the anterior aspect of the neck. It consists of two lobes connected together by a tissue band called the isthmus. The lobes lie on either side of the trachea and the larynx, between the cricoid cartilage and the suprasternal notch. There is commonly a third lobe, called the pyramidal lobe extending from the upper part of the isthmus towards the hyoid bone. The thyroid receives its blood supply mainly through the superior and inferior thyroidal arteries, the former a branch of the external carotid artery and the latter a branch of the thyrocervical trunk. The venous blood is drained via the internal jugular vein and the brachiocephalic vein. The normal weight of the thyroid in an adult ranges from 12-20 g, depending on the body size and iodine supply (Fig. 1).

![The thyroid gland diagram]

Figure 1 The thyroid gland

3.2 EMBRYOLOGY

The formation of the thyroid gland begins at about the end of the third week after fertilisation. It appears as a median endodermal part of the floor of the primitive pharynx and grows downwards in the neck while forming the bilobular structure, which
INTRODUCTION

is completed in the third trimester. The follicular cells, originating from epithelial cells located in the base of the tongue (foramen caecum) fuse with the neuroendocrine C-cells while descending to the neck. The thyroid hormone receptors are present in the brain of the human foetus from the 8th to the 10th week of gestation. The thyroid begins to accumulate iodine after the 11th week of gestation.

3.3 PHYSIOLOGY

The thyroid hormones, triiodothyronine (T₃) and thyroxine (T₄), are synthesized by the follicular epithelial cells of the thyroid gland. This synthesis requires iodine and synthesis is increased by stimulation of thyroid-stimulating hormone (TSH) from the anterior pituitary gland.

In the basement membrane of the follicular cells there is an iodide pump, NIS (NA⁺/I⁻ symporter) which pumps iodide into the cell. In the cell, iodide is oxidised by a peroxidase to the more reactive iodine, which reacts with tyrosine on a thyroid glycoprotein called thyroglobulin (Tg), to form mono-iodotyrosine (MIT) or di-iodotyrosine (DIT) thyroglobulin. MIT and DIT are then coupled to form T₃ or T₄ still attached to thyroglobulin, which is stored in the colloid. Two DIT are combined to form T₄ and one MIT is coupled with one DIT to produce T₃. The general reaction can be described by the formula: \( I + H₂O₂ + Tg \rightarrow Tg\ (MIT, DIT) \rightarrow Tg\ (T₄, T₃) \). Under stimulation by TSH, colloid droplets are taken back up into the cell by endocytosis, where they fuse with lysosomes and the thyroglobulin is proteolysed to release the iodinated residues from the glycoprotein. The remaining MIT and DIT are deiodinated and the liberated iodine is recycled in the follicle cell (Fig. 2). Before release some of the T₄ is converted to T₃.
Figure 2 The follicular cell

Most T\textsubscript{3} (80-85\%) derives from extrathyroidal conversion of T\textsubscript{4} in peripheral tissue, predominantly in the liver and kidney. The rest of the circulating T\textsubscript{3} is secreted directly from the thyroid. Iodine that is liberated from thyroid hormone is excreted in the urine or recirculated to the thyroid, where it is concentrated by the trapping mechanism (NIS).

T\textsubscript{3} is about ten to fifteen times more active than T\textsubscript{4} owing to its higher affinity for the intranuclear thyroid hormone receptors. The thyroid secretes mostly T\textsubscript{4}, and the ratio of T\textsubscript{4}:T\textsubscript{3} is about 20:1. Less than 1\% of the total circulating amount of each hormone is free in the plasma (fT\textsubscript{3} and fT\textsubscript{4}). The half-life of T\textsubscript{4} in the plasma is about 6-7 days and that of T\textsubscript{3} about 1 day.

The thyroid also produces the hormone calcitonin, which is secreted by the parafollicular C-cells. This hormone plays a role in calcium homeostasis.\textsuperscript{4}
INTRODUCTION

Thyroid hormone activity is regulated through the hypothalamic-pituitary-thyroid-peripheral tissue axis. The hypothalamus releases the thyrotropin releasing hormone (TRH), which stimulates the pituitary gland secretion of the TSH. The syntheses of thyroid hormones are stimulated by TSH, and are regulated by a feedback system whereby T₃ and T₄ decrease the release of TRH and TSH (Fig. 3).

**Figure 3** The hypothalamic-pituitary-thyroid axis. Negative hormonal feedback regulation by thyroid hormones is indicated by a negative sign. Events with a positive effect on thyroid hormone synthesis and release are marked with a positive sign.
3.4 EPIDEMIOLOGY OF HYPERTHYROIDISM

Hyperthyroidism is a common disease and affects approximately 2 % of women and 0.2 % of men worldwide.\textsuperscript{6,7} In Scandinavia the prevalence of hyperthyroidism in females is about 2.5 %. The patients are usually between the ages of 20-50 years at onset of the disease, depending on the endemic iodine intake.\textsuperscript{1} The most common types of hyperthyroidism in Sweden are Graves’ disease (GD) (60 % - 70%), toxic multinodular goiter (TMNG) and Solitary toxic adenoma (STA) (Table 1). Among the younger patients Graves’ disease occurs most frequently, while among older patients TMNG and STA are more common.

The incidence of hyperthyroidism is reported from different studies to be between 23.6 - 43.0 per 100 000 per year in different studies.\textsuperscript{8-14} We have recently found an annual incidence of hyperthyroidism in the county of Stockholm of 32.7/100000 (paper I, Abraham-Nordling et al, 2008).

Factors such as the geographical area (country), time period and type of study method may explain these variations in the results of the different studies. Other factors for example age, gender, family history, smoking habits, stress and iodine status, contribute to the development of thyrotoxicosis.\textsuperscript{15-17}

3.5 SUBGROUPS OF HYPERTHYROIDISM

The term thyrotoxicosis means that excessive amounts of thyroid hormones (T\textsubscript{3} and T\textsubscript{4}) are circulating outside the thyroid gland. The definition pays no consideration to the background of the condition. Hyperthyroidism refers to the signs and symptoms of overproduction/-secretion of thyroid hormones by the thyroid, which leads to an overactive body metabolism (body burns calories and energy).\textsuperscript{18} If too small amount of thyroid hormones are produced, the result is hypothyroidism.\textsuperscript{19,20} It is important to determine the specific cause of the thyrotoxicosis, as it is the aetiology that decides the treatment strategy (Table 1).

There are three main types of hyperthyroidism caused by increased thyroid hormone production: Graves’ disease, toxic multinodular goitre and solitary toxic adenoma.
### Table 1 Subgroups of thyrotoxicosis. Hyperthyroidism subtypes are marked with *

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogenesis</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Graves’ disease (GD)</strong> *</td>
<td>Autoimmune, Thyroid-stimulating antibody against the TSH receptor</td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Toxic multinodular goitre</strong> (TMNG) *</td>
<td>Autonomous functioning of thyroid</td>
<td>Common</td>
</tr>
<tr>
<td>(Plummer’s disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solitary toxic adenoma</strong> (STA)*</td>
<td>Autonomous functioning of thyroid</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Thyroiditis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acute</td>
<td>Inflammatory processes leads to release of thyroid hormones</td>
<td>Common/Rare/Uncommon</td>
</tr>
<tr>
<td>(bacterial, fungal infection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Subacute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(post-viral infection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Amiodarone-induced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(high iodine content leads to inflammation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Post-partum or painless</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(autoimmune)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thyrotoxicosis factitia</strong></td>
<td>Ingestion of T₄ and/or T₃</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Iodine-induced</strong></td>
<td>Iodine ingestion, Radiographic contrast agent, Amiodarone</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Human chorionic gonadotropin (hCG)</strong></td>
<td><strong>hCG stimulation of TSH receptor leads to an increase in T₄ or T₃ and a decrease in TSH</strong></td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>hyperthyroidism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neonatal hyperthyroidism</strong></td>
<td>Transplacental passage of TSH receptor antibodies</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Pituitary resistance to thyroid hormones</strong></td>
<td>Unclear aetiology</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Rare malignancies</strong></td>
<td>E.g. thyroid cancer, struma ovarii</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>TSH- secreting pituitary tumour</strong></td>
<td>Autonomous TSH secretion from pituitary adenoma</td>
<td>Very rare</td>
</tr>
</tbody>
</table>
3.5.1 Graves’ disease

Graves’ disease is the most common type of hyperthyroidism and accounts for approximately 60-70 % of all cases.\(^{21}\) It is an autoimmune disease and is caused by autoantibodies that target the TSH receptors and activate them.\(^{22}\)

Graves’ disease is more common among women, with a female to male ratio of approximately 7-10: 1.\(^{6}\) Patients with Graves’ disease can have thyroid gland disorders such as goitre, pretibial myxoedema which occurs in 0.5 – 4 % of GD patients, and thyroid acropachy, which occurs in 0.1 to 1 % of patients with GD; in addition symptoms that are associated only through the immunological thyroid associated ophthalmopathy (TAO) occurs in 10-25%.\(^{23}\)

The ophthalmopathy can include periorbital edema, conjunctival irritation, proptosis, ophthalmoplegia and visual impairment. The pathophysiology of TAO is unclear and a pathogenic link between GD and the ophthalmopathy has not been identified.\(^{24}\) Several studies have shown that the level of thyrotropin receptor (TSHR) is higher in orbital adipose tissue from patients with TAO than from patients without TAO. These findings suggest that TSHR might be involved in the development of ophthalmopathy development \(^{25-27}\). Furthermore, smoking has been shown to be strongly associated with the development of TAO.\(^{21, 18, 28, 29}\) Most cases of TAO consist of mild ocular manifestations, about 18 % of the patients have severe symptoms with intensive pain and double vision and diploia 3% - 5% have visual impairment. TAO can also occur without Graves’ disease. The patients with severe symptoms require medical treatment such as glucocorticoids and in selected cases orbital radiotherapy, or orbital decompressive surgery. In many cases without inflammatory TAO, such as lid retraction and lid-lag, specific medical treatment is not required.

3.5.2 Toxic multinodular goitre

The prevalence of TMNG varies in proportion with the endemic iodine sufficiency and is higher in areas with greater insufficiency of iodine. TMNG is considered to evolve in an atoxic multinodular thyroid gland, which subsequently develops autonomously functioning nodules over time.\(^{1}\) The pathophysiology is thought to be attributable to somatic mutations in the TSH receptor gene, causing constitutive TSH receptor activation.\(^{30-32}\)
INTRODUCTION

TMNG is mostly present in patients older than 50 years of age, who have previously had a long history of multinodular goitre. The thyrotoxic symptoms are usually mild. Since the patients are of older age, TMNG often presents with cardiovascular manifestations of thyrotoxicosis, such as palpitations, tachycardia and atrial fibrillation. The diagnosis is made through laboratory evaluations that show suppressed TSH and elevated T3 and/or T4. Radioactive iodine uptake and scanning reveals normal or increased uptake with focal areas of increased uptake corresponding to hyperfunctioning nodules.1

3.5.3 Solitary toxic adenoma
Like TMNG, the pathogenesis of STA is thought to be attributable to a mutation in the TSH receptor gene, causing constitutive receptor activation. The disease progresses slowly and nodule autonomy occurs after it has been present for many years. STA is most often seen in patients over 50 years of age. Laboratory evaluation demonstrates suppressed TSH and elevated T₃ and T₄. In some cases STA causes isolated “T₃-toxicosis”, and in those cases the T₄ can be upper-normal with an elevated T₃. Radioactive iodine uptake and scanning shows increased uptake over the nodule, and suppressed uptake throughout the remainder of the gland.33, 34
3.6 SYMPTOMS AND DIAGNOSIS OF HYPERTHYROIDISM

The patients have symptoms and signs related to excess thyroid hormone concentrations in the cell. This leads to a hypermetabolic state, resulting in an imbalance of energy metabolism, in which energy production exceeds energy expenditure. Typical symptoms are weight loss, palpitations, heat sensitivity, fatigue and nervousness or anxiety. Clinical findings such as tachycardia, enlarged thyroid, warm moist skin and slight tremors are common. Other symptoms and signs are muscle weakness and vertebral compression due to osteoporosis.

In Graves’ disease there may be additional symptoms such as ophthalmopathy, double vision, pretibial myxoedema, acropathy and myopathy. The immunological-associated ophthalmopathy affects 10-25% of the patients. Many symptoms of TAO are explained by an increase in the volume of both the orbital fat, connective tissue and the extraocular muscle bodies in the orbit. The symptoms may begin before, at or after the onset of Graves’ hyperthyroidism.

Women sometimes have irregular menstrual periods and decreased fertility. About 25-35 % of elderly people with hyperthyroidism will develop atrial fibrillation that is resistant to treatment until the underlying hyperthyroidism has been corrected. Hyperthyroidism may also cause neuropsychiatric symptoms such as restlessness, agitation, anxiety, emotional lability and even psychosis.

*Thyroid storm* is an unusual and life-threatening situation, with signs such as tachycardia (>140 beats per minute), atrial fibrillation, fever, agitation, abdominal pain, vomiting and diarrhoea, psychosis or coma. These symptoms may begin after trauma, childbirth, infection or surgery in patients with hyperthyroidism but may also occur in patients who have not previously been diagnosed with thyroid disease.

Hyperthyroidism is diagnosed from suppressed thyrotropin (TSH), and elevated levels of thyroid hormones; fT₄ and fT₃. Laboratory findings may also include elevated AST, ALT and ALP, hypercalcemia, and decreased cholesterol levels. Assays of free thyroid hormones are mainly used for the diagnosis, since they are not affected by changes in plasma binding protein concentrations, as in infectious hepatitis, during
INTRODUCTION

pregnancy and in patients taking oestrogens or opiates. Assay of the total $T_3$ or $T_4$ measures mainly the protein-bound hormone. Only $\leq 1\%$ of the $T_4$ and $T_3$ circulates in the free form, as both $T_4$ and $T_3$ are tightly bound to transport protein. $T_3$ is by far the most metabolically active of the thyroid hormones. For diagnosis of Graves’ disease thyroid receptor antibodies (TRAb) need to be taken. These are present in 99% of the cases.

Thyroid scintigraphy with radioiodine or technetium, the clinical appearance and the laboratory results are the key tools that are used to determine the aetiology of thyrotoxicosis and to visualise the thyroid structure and function. In the 24-hour radioactive iodine uptake test a radioactive isotope of iodine (131-I) is used and the uptake is measured at 6 and 24 hours after dosing. Increased isotope uptake is seen in patients with Graves’ disease, TMNG and STA. A diffuse uptake throughout the gland signifies Graves’ diseases. Hyperfunctioning nodules with increased uptake indicate toxic nodular goitre. Solitary toxic nodules have a radioiodine scan pattern demonstrating increased uptake in the hyperfunctioning nodule and decreased uptake in the remainder of the gland at scintigraphy. Increased 24-hour uptake of 131-I can be observed in conditions other than hyperthyroidism, such as significant iodine deficiency. With chronic iodine deficiency, there is an increase in iodine uptake by the thyroid gland to compensate for the low circulating iodine concentration. Conditions typically associated with decreased radioactive iodine uptake are exogenous thyroid hormone uptake, thyroiditis in the destructive phase, and iodine-induced thyrotoxicosis.

Thyroid ultrasonography is useful for identifying the presence of cysts, or of single or multiple nodules. Computed tomography (CT) or magnetic resonance tomography (MR) is performed to determine the anatomy of the thyroid and is mainly used before surgery.
3.7 TREATMENT OF HYPERTHYROIDISM

The choice of treatment for hyperthyroidism varies with the severity of the illness and local traditions.\textsuperscript{48-51} There are three main treatments for patients with hyperthyroidism, namely antithyroid drugs (ATD), surgery and radioiodine. Medical treatment blocks the hormone synthesis and as well blocking the peripheral conversion of T\textsubscript{4} to T\textsubscript{3}. Surgical treatment involves partial or total surgical ablation of the thyroid. Radioiodine, \textsuperscript{131}I, concentrates in the thyroid gland and destroys the thyroid.

For Graves’ disease patients all three treatments can be used. In the USA, radioiodine therapy is the preferred treatment for Graves’ patients, whereas in Asia and Europe, antithyroid drug therapy is preferred.\textsuperscript{52} For patients with toxic nodules or toxic adenoma the definitive treatments are radioiodine or surgery (Table 2).

3.7.1 Antithyroid drug

In Sweden mainly two drugs are used, tiamazol (Thacapzol\textsuperscript{®}) and propylthiouracil (Tiotil\textsuperscript{®}).\textsuperscript{1} Propylthiouracil has the advantages over tiamazol that it inhibits the conversion of T\textsubscript{4} to T\textsubscript{3} and leads to a faster decrease in the levels of activated thyroid hormone. It is also the treatment of choice in pregnant and lactating women.\textsuperscript{53} The use of antithyroid drugs leads to inhibition of thyroid hormone synthesis. In general this therapy is most useful in young patients with a small gland and mild disease. Antithyroid drug therapy is given to pregnant women (propylthiouracil), and as pretreatment in patients who are going to be treated surgically or with radiiodine.\textsuperscript{54} Although an autoimmune mechanism is responsible for Graves’ disease, success in controlling the hyperthyroidism usually has positive effects with diminishing TRab levels.

The duration of the treatment with an antithyroid drug in Graves’ diseases is 12 to 18 months and sometimes even a longer period is required. The risk of relapse with this therapy in Graves’ patients is 40-60 %.\textsuperscript{55-58}

In patients with toxic nodular hyperthyroidism or toxic adenoma, inhibition of the thyroid hormone production only occurs during the treatment with ATD, and the increased hormone production usually returns when the therapy is stopped. This
therapy is therefore not the first treatment of choice. If the patient is old and surgical or radioiodine treatment cannot be carried out the patient may be treated with a low dose of antithyroid drug for the rest of his life.

Antithyroid drug therapy is either given alone in a low dose or given in a high dose in combination with Levothyroxin for the whole treatment period.\textsuperscript{59} The most serious reaction to antithyroid drugs is agranulocytosis, which requires immediate cessation of all ATD therapy. The symptoms of agranulocytosis are sore throat and fever. Other reactions to antithyroid drugs are rash, arthralgia and gastrointestinal symptoms such as hepatotoxicity.

\section*{3.7.2 Radioiodine}

In iodine-131 (radioiodine) therapy, radioactive iodine is given orally (either as a pill or in liquid form) on a one-time basis to destroy the function of a hyperactive gland. The cells of the thyroid pick up the radioactive iodine, which destroys them. Before radioiodine is given, a 24-hour 131-I uptake test with estimation of $t\frac{1}{2}$ of 131-I by measurement after 5-7 days is performed. Together with estimation of the thyroid volume, the treatment dose of 131-I can thus be calculated. The treatment is safe and cost-effective\textsuperscript{60}, but causes permanent hypothyroidism in virtually all patients and the need for life-long T\textsubscript{4} replacement.\textsuperscript{61, 62}

The goal of the use of radioiodine is to administer enough radiation to cure the patient’s hyperfunction and, dependent on the indication, to achieve either permanent hypothyroidism or euthyroidism (see below). There is much individual variability in response to the treatment with radioiodine. In Graves’ disease, the usual aim of the treatment is to render the patient permanently hypothyroid with one treatment. This is achieved in approximately 80 \% of the patients within 6 months.\textsuperscript{63} In about 20 \% of the patients need more than one 131-I treatment. Total ablation of the thyroid function is the best assurance that there will be no recurrence later in life.

The effect of 131-I treatment is not immediate, but usually the patient becomes hypothyroid within 2-3 months after treatment. However, since the mid-90s we have routinely substituted with levothyroxin after 131-I treatment of Graves’ disease to avoid development of hypothyroidism since variation in the T\textsubscript{4} level is associated with greater risk of developing TAO.\textsuperscript{63, 64} Accordingly, the serum TSH and free T\textsubscript{4}
levels should be monitored after 131-I treatment to ensure that euthyroidism has been achieved.

In TMNG and STA, 131-I therapy aims to cure the hyperfunctioning nodule(s) and hypothyroidism is less likely to occur since the iodine uptake in the normal thyroid tissue is suppressed and therefore will not be exposed to radiation to the same degree. The majority of patients therefore will become euthyroid when the suppression disappears and the thyroid hormone synthesis returns to normal \(^65\).

The frequency of leukemia or malignant lymphoma and the overall risk for malignancy after radioiodine treatment has not been shown to increase and is considered negligible \(^66-69\).

Radioiodine is the treatment of choice in patients with toxic nodular goitre and Graves’ disease. The use of radioiodine treatment varies within and between different countries. In the USA, this treatment is for example used, as the primary treatment in most adults with Graves’ disease and is given from the age of 21 years.\(^{50}\) In Sweden it is not given to young adults. Radioiodine is strongly contraindicated in pregnancy and in breastfeeding mothers. Women who have received radioiodine treatment should avoid becoming pregnant within 12 months after treatment.

It has been shown that use of radioiodine in patients with “unstable or progressive” Graves’ ophthalmopathy may lead to development or worsening of TAO compared with antithyroid drug therapy or surgery, especially in patients with aggressive hyperthyroidism and in smokers.\(^{64,70}\) Early administration of thyroxine or treatment with high-dose steroids at the time of \(^{131}\)I treatment can reduce the risk of deterioration of the ophthalmopathy.\(^{71,72}\)

Approximately 10 % of radioiodine-treated patients develop hyperthyroidism due to radiation-related thyroiditis which can occur a few weeks after treatment. The symptoms may be relieved by therapy with beta-blockers.

### 3.7.3 Surgery

Indications for surgical treatment are Graves’ disease in young adults, patients with a poor response to antithyroid drugs, a large goitre, and patients with severe Graves’ ophthalmopathy. Patients with Graves’ disease and thyroid nodules with suspect
INTRODUCTION

malignancy (approximately 20 % of nodules in patients with Graves’ disease are thyroid cancer), pregnant women who are not controlled by antithyroid drugs or who wish to become pregnant soon after treatment, and patients who have local compressive symptoms such as pain or dysphagia are candidates for surgical treatment. Surgery performed by an experienced surgeon is safe, but the complications are permanent hypoparathyroidism and recurrent laryngeal nerve damage, which occurs in 1% of the patients.

There are two types of surgical procedures, total or subtotal thyroidectomy. Subtotal thyroidectomy is mainly preferred, to avoid nerve damage and hypothyroidism. The patients should be euthyroid before surgery, an antithyroid drug either alone or in combination with iodine. Beta-blockers alone are not adequate and are only used if surgery is urgent.

**Iodine**

In severe Graves’ disease, where $^{131}$I or ATD therapy is not feasible, a 5 % iodine-potassium iodide solution in large doses (3 x 11 mg increasing to 165 mg x 3 daily) can be administered orally 7-10 days immediately before surgery. Iodine will decrease the thyroid hormone synthesis (Wolff-Chaikoff effect) and the vascularisation of the thyroid gland and thereby make it easier and more safe for the surgeon. However, it is important that surgery is performed within this time frame since the thyroid hormone synthesis will otherwise escape the blocking effect of iodine, possibly causing an abrupt increase in serum thyroid hormone levels and aggravation of the hyperthyroidism.

**Beta-blockers**

Beta-blockers such as propranolol diminish common symptoms of increased adrenergic activity in hyperthyroidism, such as palpitations, trembling, and anxiety. However, beta-blockers do not have substantial curative effects on the disease process.
Table 2 Summary of treatment of hyperthyroidism. (ATD = antithyroid drugs)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATD</td>
<td>Children (GD with moderately high thyroid hormones)</td>
<td>Non-invasive</td>
<td>Low cure rate (average 40-60%)</td>
</tr>
<tr>
<td></td>
<td>Pre-operative and $^{131}$I treatment</td>
<td>Low risk of hypothyroidism</td>
<td>Adverse drug reactions</td>
</tr>
<tr>
<td></td>
<td>Pregnancy and breastfeeding</td>
<td>Lower initial cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GD with complicated ophthalmopathy</td>
<td>Possible to remissions due to immune effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Older patients (also toxic multinodular goitre and adenoma) when no other treatment is possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radio-iodine ($^{131}$I)</td>
<td>Older patients</td>
<td>Most cost-effective</td>
<td>Often hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Relapse after ATD</td>
<td>High cure rate with single-dose treatment</td>
<td>No pregnancy for 12 months, no breast feeding</td>
</tr>
<tr>
<td></td>
<td>GD patients without ophthalmopathy</td>
<td></td>
<td>Small risk of hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Nodular goitre with pressure symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toxic adenoma (alternative to surgery)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relapse after surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Pregnancy and Children</td>
<td>Rapid and effective</td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Side-effects of ATD</td>
<td></td>
<td>Complications recurrent laryngeal nerve damage, hyperparathyroidism, bleeding</td>
</tr>
<tr>
<td></td>
<td>Relapse after ATD or $^{131}$I</td>
<td></td>
<td>Permanent hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Patients who refuse $^{131}$I or low iodine uptake</td>
<td></td>
<td>Most costly</td>
</tr>
<tr>
<td></td>
<td>Co-existing suspicious malignant nodule</td>
<td></td>
<td>Scar</td>
</tr>
<tr>
<td></td>
<td>Large goitre</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toxic adenoma (first-line treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GD with clear ophthalmopathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.8 QUALITY OF LIFE AND SUICIDE

There is no general consensus on the definition of health-related quality of life (HRQoL). HRQoL is related to the patient’s physical, psychological and social well being that is influenced by treatment or by a medical condition.\textsuperscript{81, 82} In this thesis the term QoL is used to refer to HRQoL.

The parameters of Qol have different cultural meanings. A World Health Organization project has developed the WHOQOL, which is a multi-lingual assessment of quality of life in different languages that is directly comparable.\textsuperscript{83} The concept of QoL can be used to obtain information both in clinical practice and research to decide upon treatment or to evaluate clinical treatment results and prognostic factors. These instruments are widely used in international clinical trials, marking a new phase of research.\textsuperscript{84} The transformation of the QoL concept from speculation to a respected clinical endpoint is evident from the number of publications on studies that have included a QoL. During the 1980s approximately 300 such reports were published, and today this figure is almost 10 000.

There are two types of questionnaires, generic and disease-specific questionnaires.\textsuperscript{85, 86} In many reports more than one questionnaire is used to test a proposed hypothesis. The thyroid disease and TAO specific questionnaires are: \textbf{a}) Hyperthyroidism Complaint Questionnaire (HCQ),\textsuperscript{87} \textbf{b}) Graves Ophthalmopathy QoL questionnaire (GO-QOL),\textsuperscript{88} \textbf{c}) 90-item TAO-specific questionnaire,\textsuperscript{89} \textbf{d}) Chronic Thyroid Questionnaire (CTQ),\textsuperscript{90} \textbf{e}) Thyroid symptom Questionnaire (TSQ),\textsuperscript{91} and \textbf{f}) Underactive Thyroid-Dependent QoL Questionnaire (ThyDQoL).\textsuperscript{92} These available questionnaires lack documented relevant QoL issues and most of them except GO-QOL lack validation. None of the questionnaires has the potential to cover all aspects relevant to patients in longitudinal studies, where patients may shift from one thyroid state to another as a result of natural history or treatment.\textsuperscript{93}

To measure health-related quality of life, QoL in the present thesis was assessed with the generic and standardised Medical Outcome Study SF-36 Short Form Health Survey and QoL2004 (see appendix). The SF-36 is designed to allow assessment involving generic health concepts that are not specific to any age, disease or treatment
The emphasis is upon physical, social and emotional functioning. The Short Form-36 (SF-36) Health Survey is one of the most widely used, self-administered questionnaires for generic health status or health-related quality of life. There are 36 questions addressing eight concepts (scales) of health: physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role-emotional (RE) and mental health (MH). The first four scales (PF, RP, BP, GH) are referred to as the physical part of QoL, while the latter four scales (VT, SF, RE, MH) are referred to as the mental part of the QoL concept. To reduce the number of outcome measures, two summary components have been extracted from the eight original scales. The physical component summary (PCS) score and the mental component summary (MCS) score. The Swedish version of the SF-36 is well documented and has shown good psychometric qualities in different groups. All scale scores range from 0 to 100, with 100 representing optimal physical functioning and well-being. The mean score is 50 and the standard deviation (SD) is 10.

Mental symptoms such as nervousness, anxiety, poor concentration and personality changes are pronounced in hyperthyroidism. Long-term neuropsychiatric symptoms following hyperthyroidism have also been found to occur, even when the patients have been successfully treated. Several studies have also shown that the quality of life in many patients is severely decreased at long-term follow-up. The hormonal disturbances in hyperthyroidism have important influence on the brain. Depressed patients for example have been reported to have an altered thyroid-stimulating hormone response to TRH, which it has been suggested may entail a risk of suicide. In addition, thyroid hormones may interact with important mood-modulating neurotransmitter systems such as the serotonin system.

Mental illness, moreover is the principal cause of suicide. More than 90 % of persons committing suicide have mental disorder at the time of the suicide act which is most commonly due to mood disorder. The rate of suicide varies in different countries, age groups and between the genders. In Sweden the suicide rate in 2001 was 13.4/100 000. The rate for males was 18.9/100 000 and among females 8.1/100 000. Men commit suicide at a higher rate than women, and the male to female ratio is approximately 3-4:1 (World Health Organization, 2005).
4 AIMS OF THE THESIS

The aims of the present thesis were:

- to determine the total and age-specific incidence of hyperthyroidism and to identify the subgroups of hyperthyroidism (Graves’ disease, toxic uni- or multinodular goitre) in the county of Stockholm (Paper I)

- to determine whether there are any long-term differences in quality of life and state of health in patients treated differently for Graves’ hyperthyroidism and compared with a healthy reference population (Paper II)

- to determined whether the quality of life scores in SF36 and QoL2004 in Graves’ hyperthyroidism patients may have been influenced by the current thyroid hormonal status or the level of L-thyroxine (T4) substitution (Paper III)

- to investigate the risk of suicide among patients with hyperthyroidism compared with a general Swedish age- and sex matched population (Paper IV)
PATIENTS AND METHODS

5 PATIENTS AND METHODS

5.1 PAPER I

In this paper the patients diagnosed with hyperthyroidism during the years 2003-2005 in the county of Stockholm, Sweden, was a registered prospectively. Before the study was started, all the hospital specialists (Hyperthyroidism Incidence Study Group in Stockholm, see paper I) were notified and a questionnaire was circulated to optimise its content (see Appendix).

Patients diagnosed with hyperthyroidism (GD, TMNG and STA) for the first time during the 3-year period from January 1, 2003 to December 31, 2005 were included in the study. The registration of patients was done only at the first visit, when the patient met a specialist who confirmed the diagnosis. The mean number of residents in the region per year during the study period was 1,867,995. All patients who were ≥ 18 years of age in the Stockholm county region were registered. Patients who were under 18 years of age (22%) were excluded. The mean number of subjects in the study population during this 3-year period was therefore 1,457,036.

In Stockholm the treatment of hyperthyroidism is mainly decided upon and initiated by a specialist physician. The physicians participating in the registration were all specialists in medical endocrinology, oncology, nuclear medicine or surgery. They were working at eight specialised units/hospitals in the county of Stockholm that were participating in the registration. A letter was sent to all primary health care centres in Stockholm regarding possible patients with hyperthyroidism who had not been referred to a specialised unit, in order to ensure that all patients were included in the study.

The patients were identified by having symptoms and/or signs of hyperthyroidism in combination with elevated levels of one or several of the following thyroid hormones: total serum thyroxin (T₄), free thyroxin (fT₄), total serum triiodothyronine (T₃), free triiodothyronine (fT₃), and with suppressed thyroid-stimulating hormone (<0.02 mU/L). Screening for autoimmunity was done by measuring thyrotropin receptor antibody (TRab) and thyroid peroxidase antibody (TPOab).
PATIENTS AND METHODS

All patients with laboratory confirmed hyperthyroidism and diffuse goitre, positive TRab and/or a verifying thyroid scintigraphy showing a diffuse pattern of isotope uptake were diagnosed as having GD. All patients with laboratory confirmed hyperthyroidism and single or multinodular goitre, and absence of TRab were classified as having STA and/or TMNG. In doubtful cases this diagnosis was confirmed by scintigraphy showing locally increased isotope uptake with suppression of normal thyroid tissue in the remaining part of the gland.

Exclusion criteria were: a past or current history of hyperthyroidism, presence of destructive thyroiditis, or hyperthyroidism secondary to pharmacological treatment with amiodarone or interferon.

The following data were registered: age, sex, ethnic origin (country of birth), type of hyperthyroidism (GD, TMNG, STA), amiodarone treatment, smoking habits, and occurrence of endocrine ophthalmopathy and pretibial myxoedema. A blood sample was drawn and laboratory tests for current thyroid hormonal levels were performed. A diagnostic thyroid scintigraphy and a 24-hour $^{131}$I uptake test were carried out in selected cases. For each patient the initially planned treatment was registered.

Statistical analysis

The incidence rate was calculated on the basis of the age- and sex- matched general population. Statistica 7.1, StatSoft® , Inc. Tulsa OK, USA was used for all computer analyses.

The study was approved by the local ethics committee of Karolinska Institutet (KI: 02-520).
5.2 PAPERS II AND III

The patients in studies II and III, totally 179 patients were randomised between 1983 and 1990. The original study is often referred to as the “TT-83 study” (thyrotoxicosis and the year (1983) when the randomisation began). The patients were between the ages 20-55 years. They were randomised into five groups: young adults (20-34 years) with surgical or medical treatment and older adults (35-55 years) with surgical, medical or radioiodine treatment. The medical treatment was “block-and-replace” treatment with antithyroid drugs plus L-thyroxin for 18 months. Subtotal thyroidectomy was performed, followed by L-thyroxin therapy in the surgical treatment group. The radioiodine treatment, $^{131}$I, was given to the older adult only (Fig. 4).

Figure 4 The patients in the studies II and III. (YS=Young adults with surgical treatment, YM=Young adults with medical treatment, OS= Older adults with surgical treatment, OM= Older adults with medical treatment, OR= Older adults with radioiodine treatment)
PATIENTS AND METHODS

The follow-up period in these studies was from the last follow-up at 3 years after initiation of treatment as reported,\textsuperscript{61} to 2003. The total follow-up period in these studies was therefore 14-21 years after the initial treatment for Graves’ hyperthyroidism.

Of the total 179 patients, 7 patients had died. The remaining 172 patients received the following:

- Quality-of-life questions (SF-36, Medical Outcome Study 36-items Short Form Health Status Survey) (see Appendix).
- Treatment-related questions (QoL2004, which was used in the previous 3-year follow-up) (see Appendix).
- Additional questions as to whether other autoimmune diseases, osteoporosis, cardiac diseases or other psychosocial events not covered by SF-36 had occurred during the period in question. The psychosocial-related questions were similar to those that were used in the previous follow-up, QoL1996.\textsuperscript{61} These questions were originally designed in collaboration with experienced epidemiologists and statisticians at the Center of Statistics, National Board of Health and Welfare in Sweden.
- The subjects were asked for a blood sample, for analysis regarding the current hormonal status.

Up to the end of May, 2004, of the 172 patients included in the study II, 145 could be evaluated.

Blood samples were available from 113 of the 145 patients who answered the questionnaires. In 22 of the 113 patients, either the blood samples were analysed at another hospital with different reference ranges, or the patients had more than one treatment for hyperthyroidism, or the SF-36 or QoL2004 response was missing. These 22 patients were therefore excluded. In total, study III comprised 91 subjects in whom both blood analyses and SF-36 or QoL2004 (n=89) were available. They were grouped on the basis of the type of initial treatment, into three groups consisting of a surgical group (n= 38), a medical group (n=17) and a radioiodine group $^{131}$I (n=27). There was an additional radioiodine group consisting of nine patients who initially had had medical or surgical treatment and who later received $^{131}$I (n=9) (Fig. 4).

The study was approved by the local ethics committee of Karolinska Institutet (KI, 03-232)
**Laboratory assessment**

TSH was measured by chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA, USA, reference range 0.2–4.0 mU/l; intraassay coefficient of variation (CV) value, 3.1%; interassay CV value, 3.86%). The lower detection limit is 0.01 mU/l. fT3 was determined by time-resolved fluoroimmunoassay (AutoDELFIA Triiodothyronine, Wallac Oy, Turku, Finland), reference range 4.0–7.0 pmol/l; intraassay CV value, 3.9%, interassay CV value, 4.4%. T3 was determined by time-resolved fluoroimmunoassay (AutoDELFIA Triiodothyronine, Wallac Oy, Finland), reference range 1.1–2.5 nmol/l. fT4 was determined by chemiluminescent immunoassay (Beckman Coulter, reference range 10–20 pmol/l). Antibody to thyroid peroxidase (TPOab) was measured by chemiluminescent immunoassay (Nichols Advantage, San Clemente, CA, USA, reference range <2 kU/l; intraassay CV value, 3%, interassay CV value, 5%) and thyrotropin receptor antibody (TRab) was determined by radioreceptor antibody assay (BRAHMS, TRAB human, Henningsdorf, Germany, reference range <8 U/l).

**Statistics**

Study II: The result from the SF-36 scores comprises eight subscales, which are summary scales transformed to a range of 0–100. These can be combined with the Physical Component Summary and Mental Component Summary, which are weighted scores, constructed to mean = 50 and SD = 10. Kruskal–Wallis analysis of variance (ANOVA) by ranks was used, for measurement of the significance of the quality of life (SF-36) and the SAS System was used for analysis of QoL2004. A 95% confidence interval for the median was calculated for each SF-36 subscale within each treatment group. Assume that the median value (presented in the SF-36 manual) is the true population median for a control population. If the 95% confidence interval for the median value in the treatment group covers the median value in the control population, no systematic difference between the two populations can be demonstrated statistically.

Study III: The data were analysed using the software Statistica TM (Statsoft, Tulsa, OK, USA). Non-parametrical statistics were used (Kruskal-Wallis ANOVA by ranks, Spearman’s rank correlations, Mann–Whitney U-test and $\chi^2$- test). The associations between the subscales SF-36 and the variables, namely the four treatment groups, dose of L-T4, TRab, TPOab, TSH, T4, fT4, T3, and fT3 were assessed by stepwise logistic regression analyses for ordinal response variables, a proportional odds model. The subscales in SF-36 were categorised into
four categories, according to the percentiles 0–25, 25–50, 50–75 and 75–100%. The association between the QoL2004 question ‘Do you feel well’ and the independent variables listed above was analysed by stepwise logistic regression for binary response. The software used was SAS System 9.1 (SAS Institute Inc., Cary, NC, USA).

5.3 PAPER IV

The study cohort originally included 44 234 individuals diagnosed with hyperthyroidism between 1950 and 2005 in Sweden. As a comparison cohort, we identified 45 655 patients with a record of surgically treated atoxic goitre in the Swedish Inpatient Register between 1964 and 2005. In the study cohort there were two approximately equally sized subcohorts – one with previously investigated patients who had been treated with $^{131}$I for hyperthyroidism, and one with patients identified in the Swedish Inpatient Register as having undergone surgery for hyperthyroidism between 1964 and 2005. The two subcohorts included both Graves’ disease and toxic univariate or multinodular goitre, as well as 1 911 patients who had toxic nodular goitre with Graves’ disease.

To identify patients previously treated surgically for hyperthyroidism, we used the Swedish Inpatient Register, which was established by the National Board of Health and Welfare in 1964. The Inpatient Registry started to collect data on individual hospitalisations in the Uppsala health care region in 1964, and the coverage increased rapidly; the registry covered 60% of the Swedish population in 1969, 75% in 1978, 85% in 1983, and 100% in 1987 onwards. The cohort file was linked to the registers of Total population, Migration, and Cause of death in order to verify the validity of the National Registration Numbers (NRNs) - unique personal identifiers assigned to all Swedish residents after birth or immigration. Using the NRNs, we linked the cohorts to the registers of Total population, Migration, and Causes of death for correct censoring. We excluded 601 and 734 records in the study cohort and comparison cohort, respectively, because of erroneous NRNs or other inconsistencies revealed during the record linkages, leaving 43 633 patients in the study cohort and 44 921 in the comparison cohort with surgically treated atoxic nodular goitre patients. All cohort members were followed up from the date of the first hyperthyroidism diagnosis until death, emigration or the end of the study (31 December, 2005), whichever occurred first. Information in underlying and contributory causes of death among deceased individuals was obtained from the essentially
PATIENTS AND METHODS

complete Causes of death register, in turn based on obligatory death certificates issued by physicians.

The identification of patients who had been operated on for hyperthyroidism and non toxic goitre was made by use of the International Classification of Diseases codes (Table 3).

Table 3  International Classification of Diseases codes for hyperthyroidism and non-toxic goitre

<table>
<thead>
<tr>
<th>ICD year</th>
<th>Graves' disease</th>
<th>Toxic multinodular goitre</th>
<th>Toxic unilateral goitre</th>
<th>Non-toxic multinodular goitre</th>
<th>Non-toxic goitre simplex</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD 6 (1952-1957)</td>
<td>252.0</td>
<td>252.1</td>
<td>251</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>ICD 7 (1958 – 1963)</td>
<td>252.0</td>
<td>252.1</td>
<td>251</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>ICD 7b (1964-1968)</td>
<td>252.00</td>
<td>252.10</td>
<td>251.00</td>
<td>250.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>252.01</td>
<td></td>
<td>251.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>252.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD 8 (1969 – 1986)</td>
<td>242.00</td>
<td>242.10</td>
<td>241.00</td>
<td>240.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>242.09</td>
<td></td>
<td>241.10</td>
<td>240.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>242.20</td>
<td></td>
<td>241.99</td>
<td>240.99</td>
<td></td>
</tr>
<tr>
<td>ICD 9 (1987-1996)</td>
<td>242 A</td>
<td>242 C</td>
<td>242 B</td>
<td>240 A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>242 X</td>
<td>242 D</td>
<td></td>
<td>240 X</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>241 A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>241 B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>241 X</td>
<td></td>
</tr>
<tr>
<td>ICD 10 (1997-2008)</td>
<td>E 05.0</td>
<td>E 05.2</td>
<td>E 05.1</td>
<td>E 04.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 05.5</td>
<td>E 05.2</td>
<td>E 05.1</td>
<td>E 04.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E 05.9</td>
<td>E 05.2</td>
<td>E 05.1</td>
<td>E 04.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E 04.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E 04.9</td>
<td></td>
</tr>
</tbody>
</table>

These codes were combined with the (NOMESKO) for classification of surgical procedures and they were as fellow (1963-1996): 0810, 0811, 0814, 0815, 0820, 0825, 0826, 0831, 0849 (1997-to present date): BAA 20, BAA 25, BAA 30, BAA 40, BAA 50, BAA 60, BAA 99.

The total cohort and the Inpatient Register were cross-linked to the Cause of Death Register to identify all completed suicides during the study period ( [ICD-7] codes E971-E979 and 9639, [ICD-8 and 9] codes E950-E959, and [ICD-10] codes X60-X84 and Y870).
PATIENTS AND METHODS

We analysed the question whether co-morbid conditions would further increase the risk of suicide among hyperthyroidism patients, specifically psychiatric disorders (schizophrenia, affective disorders, anxiety, and chronic alcoholism) (ICD-8, 9: 290-319; ICD-10: F00-F99) identified from the Inpatient Register (either as main diagnosis or bi-diagnosis at discharge). Since the Swedish Inpatient Register has prospectively captured details on virtually all psychiatric hospitalisations since 1973, the analysis of psychiatric disorders was restricted to hyperthyroidism patients diagnosed between 1973 and 2003.

In order to estimate the relative risk of suicidal death among patients in our cohorts, relative to the matching general Swedish population, we calculated the standardised mortality ratio, which is the ratio of observed to expected numbers of deaths due to suicide in the respective cohorts. The expected number was calculated by multiplying the mortality rates for suicide in the general Swedish population (divided into strata of five-year age groups, gender and five-year calendar periods) by the stratum-specific person-time accrued in the cohort. We calculated 95 percent confidence intervals of the SMRs by assuming that the observed number of suicidal deaths followed a Poisson distribution. Stratified analyses were performed by gender, age at diagnosis, follow-up time from diagnosis, and calendar period of follow-up. Since the hyperthyroidism is usually more severe, has a faster onset (months) and has an autoimmune background in Graves’ disease compared with the clinically milder and slowly developing (years) toxic nodular goitre, separate analyses were performed for the two diseases.

The study was approved by the local ethic committee of Karolinska Institutet (00-043, 02-020, 2006/1098-32 and 2007/1167-32).
6 RESULTS

6.1 PAPER I

During the 3-year period from January 1, 2003 to December 31, 2005, 1,431 patients with hyperthyroidism were diagnosed and registered. The mean annual incidence of hyperthyroidism in subjects above 18 years of age was 32.7 per 100,000 (Table 4). Of those 1,431 patients, 1,130 were females and 291 were males, giving a female to male ratio of 3.9:1. Among females the annual incidence was 50.8 per 100,000 and for males it was 13.6 per 100,000.

Table 4 The total number of patients and the subgroups of hyperthyroidism (GD = Graves’ disease, TMNG = toxic multinodular goitre, STA = Solitary toxic adenoma).

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>GD</th>
<th>TMNG</th>
<th>STA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>1,431</td>
<td>1,071 (75 %)</td>
<td>146 (10 %)</td>
<td>214 (15 %)</td>
</tr>
<tr>
<td>Mean incidence (/100,000/year)</td>
<td>32.7</td>
<td>24.5</td>
<td>3.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Female</td>
<td>1,130</td>
<td>820 (73 %)</td>
<td>130 (12 %)</td>
<td>180 (16 %)</td>
</tr>
<tr>
<td>Male</td>
<td>291</td>
<td>241 (83 %)</td>
<td>16 (5 %)</td>
<td>34 (12 %)</td>
</tr>
<tr>
<td>Ratio of females: males</td>
<td>3.9 : 1</td>
<td>3.4 : 1</td>
<td>8.1 : 1</td>
<td>5.3 : 1</td>
</tr>
</tbody>
</table>

The majority of the patients were between 40 and 80 years of age. The highest of incidence of hyperthyroidism among female patients was found in the age group 70-79 years (68.3/100,000/year). In male patients there was a tendency towards an increase in trend with age, with the highest peak in patients over 90 years of age (31.9/100,000/year) (n=3 patients) (Fig. 5).
Figure 5 Annual incidence of hyperthyroidism by age-and sex.

The highest annual incidence of Graves’ disease was noted in middle-aged patients; the peak incidence (29.4 per 100 000 per year) was seen in the group 30-39 years old (Fig 6). The annual incidence of TMNG and solitary toxic adenoma (STA) increased with age. For TMNG and STA the peaks were at the age group 70-79 years (TMNG 12.5 per 100 000 per year; STA 17.1 per 100 000 per year) (Fig. 6).

Figure 6 Annual incidence of subgroups of hyperthyroidism in different age groups.
(GD=Graves’ disease, TMNG = toxic multinodular goitre, STA = Solitary toxic adenoma).

Among the 1071 Graves’ disease patients, there were 820 females and the majority of the patients were between the ages of 30 and 60 years. In females the incidence of Graves’s disease decreased with increasing age.
RESULTS

6.2 PAPER II

Totally 145 patients answered the questionnaire and could be evaluated. There were no sex differences in the number of responses within the five groups, and the results are therefore given as a total for each of the five groups. The respond to the SF-36 questionnaire were analysed to see if there were any differences between the groups and were compared with those from age-matched normal subjects from a large Swedish reference population of more than 8,000 subjects. Since 14-21 years have passed since the study participants were included in the study (at 20-34 years and at 35-55 years), the SF-36 responses were compared with present appropriate health-reference groups of ages 35-54 and 50-74 years.

SF-36

Young adults (20-34 years): No treatment-related differences were found between the two young study groups (medical and surgery) with respect to the overall Physical and Mental Component Summary, or any statistical differences in the responses for any of the particular subgroups, physical (Physical Functioning, Role Physical, Bodily Pain, General Health) or mental (Vitality, Social Functioning, Role-Emotional, Mental Health) (Fig. 7a and b).

When the results were compared with those from the normal Swedish reference population a statistical by significantly lower score for Vitality was found for both the medical and surgical treatment groups (p < 0.05). The Mental Component Summary was also lower (p < 0.05) in both groups. The medical group also showed a significant lower mental health score (p < 0.05) compared with the Swedish reference population (Fig. 7a and b).
RESULTS

Figure 7 a and b Results from the SF-36 questionnaire for the young treatment groups (medical or surgery) and for the age-matched corresponding Swedish reference population. * p < 0.05 compared with the age-matched Swedish reference population.

Older adults (35-55 years): No treatment-related differences were found between the three older study groups (medical, surgery or radioiodine) with respect to the overall Physical and Mental Component Summary, or any statistical by significant differences in the responses for any of the particular subgroups, physical (Physical Functioning, Role Physical, Bodily Pain, General Health) or mental (Vitality, Social Functioning, Role- Emotional, Mental Health) (Fig. 8a and b).
RESULTS

Compared with the normal Swedish reference population, a lower Vitality score was seen for all three treatment groups (p < 0.05). The medically treated group had a significantly lower Mental Component Summary than the reference population. The radioiodine group had a significantly lower General health score (p < 0.05) (Fig. 8a and b).

Figure 8a and b Results from SF-36 questionnaire in the older treatment groups (medical, surgery or radioiodine) and in the age-matched corresponding Swedish reference population. * p < 0.05 compared with the age-matched Swedish reference population.
**QoL2004**

There were no differences between the three treatment groups except regarding the question whether the patient had undergone examination for osteoporosis. The older age groups (medical, surgery and radioiodine) had been more thoroughly examined for osteoporosis than the young groups (medical and surgery) ($p < 0.04$). No increased frequency of osteoporosis was observed in any group. There was no increase in autoimmune diseases in any of the five 5 groups.

**6.3 PAPER III**

Since there were no significant differences in age or sex in the results of study II, the results were grouped on the basis of the mode of initial treatment in this study. In total this study comprised 91 patients, 38 treated surgically, 17 medically, 27 with radioiodine, $^{131}$I and 9 with $^{131}$I in addition to medical therapy.

**SF-36 in relation to thyroid hormone status**

The scores of PCS and MCS in relation to serum TSH showed no differences among the groups. A large proportion of patients had suppressed TSH and scores lower than 50 as well as over 50. This observation was made in all four groups. There were no significant differences between the four treatment groups in PCS ($p=0.97, n=91$) or in MCS ($p=0.76, n=91$) (Fig. 9), and the analyses were therefore performed on the whole study group. Calculation based on the whole group showed no statistically significant difference between the normal and the suppressed-TSH group in median PCS and MCS.
RESULTS

![Graphs showing PCS and MCS scores in relation to log serum TSH in different treatment groups](image)

**Figure 9** Physical component summary (PCS) and Mental component summary (MCS) scores in relation to log serum TSH in the treatment groups. The area between the dotted lines indicates the reference range for TSH (0.2–4.0 mU/l, log reference range 0.69 to 0.6). Note the different scales on the X-axis.

The correlation of the SF-36 scores to serum TSH in patients without T4 substitution was also analysed. It was found that 16 patients had no T4 substitution, and in these patients the analyses showed no significant differences in the distributions of PCS or MCS above or below the average reference of 50 in relation to suppressed or normal TSH.

The correlation of the SF-36 scores to serum TSH in patients with T4 substitution showed that 74 patients had T4 as hormone replacement therapy. In 31 cases this substitution had resulted in euthyroidism with normal serum TSH, and in 41 cases suppressed TSH and subclinical exogenous thyrotoxicosis. Here again the analyses of the PCS and MCS distribution above or below 50 in patients with TSH under < 0.02 nU/l showed no statistically significantly difference from PCS or MCS above or below 50 for patients with normal TSH between 0.2 and 4.0 mU/l.
RESULTS

A correlation was found between MCS and serum fT\(_3\) in the whole group (p <0.02), but not between PCS and fT\(_3\).

*QoL2004 in relation to thyroid hormone status*

From the questionnaire responses we studied the possible correlation between the question “Do you feel well now” and serum TSH, fT\(_3\) and fT\(_4\). No significant difference in the answers “yes” or “no” between suppressed and normal serum TSH, fT\(_3\) or fT\(_4\) (\(\chi^2\)) was found. A multivariate analysis was performed and no significant correlation was observed between the variables and the question.

**6.4 PAPER IV**

In the total hyperthyroidism cohort the diagnosis of *Graves’ disease* had been given to 25 391 patients, 16 331 were classified as having *toxic nodular goitre* and 1 911 were recorded with both *toxic nodular goitre* and *Graves’ disease*. The comparison cohort (*operated on for atoxic nodular goitre*) included 44 921 patients.

In order to estimate the relative risk of suicidal death among patients in our cohorts, relative to the matching general Swedish population, we calculated the SMR, which is the ratio of observed to expected numbers of deaths due to suicide in the respective cohorts.

In the study group a total of 134 (30 male, 104 female) suicide deaths were identified versus 108 expected, corresponding to an overall SMR of 1.24 (95% CI 1.04 - 1.47) (Table 5). The corresponding numbers in the comparison cohort were 102 observed suicide deaths, 111 expected, and an SMR of 0.92 (95% CI 0.75-1.11).

In the study cohort of patients with hyperthyroidism, the excess mortality due to suicide was seemingly confined to women (SMR=1.41, 95% CI 1.16-1.71), while the point estimate of SMR among men (0.86, 95% CI 0.58-1.23) was below unity. The excess in the study cohort was concentrated to the first 5 years after diagnosis of hyperthyroidism (45 observed deaths versus 30 expected, SMR=1.51, 95% CI 1.10-2.02). Elevation just short of statistical significance was noted even 15 years or more after the diagnosis of hyperthyroidism (SMR=1.34, 95% CI 0.98-1.79). Among women with hyperthyroidism, the excess mortality
RESULTS

due to suicide was substantial in the first 5 years following diagnosis (37 deaths versus 20 expected, SMR=1.84, 95% CI 1.29-2.53) and the relative risk was also significant after 15 years or more (SMR=1.49, 95% CI 1.03-2.08).

Stratification into Graves’ disease versus toxic nodular goitre revealed that the excess was essentially confined to the former SMR 1.35, (95% CI 1.07-1.66), while the SMR for the latter was 1.06 (95% CI 0.77-1.43) (Table 5).

The mean age at entry was 51.3 years in the study group and 50.5 years in the comparison cohorts. Women were in the majority (84 percent) in both cohorts.

Table 5 Standardised mortality ratios (SMR) and 95% confidence intervals (CI) for suicide among 43 633 Swedish patients treated with $^{131}$I or surgery for hyperthyroidism between 1950 and 2005.

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Observed no. of suicide cases</th>
<th>Expected no. of suicide cases</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All hyperthyroid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>36 743</td>
<td>104</td>
<td>73.5</td>
</tr>
<tr>
<td>Men</td>
<td>6 890</td>
<td>30</td>
<td>34.8</td>
</tr>
<tr>
<td><strong>Time after diagnosis of hyperthyroidism (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>45</td>
<td>29.8</td>
<td>1.51 (1.10-2.02)</td>
</tr>
<tr>
<td>5-9</td>
<td>22</td>
<td>25.4</td>
<td>0.86 (0.54-1.31)</td>
</tr>
<tr>
<td>10-14</td>
<td>22</td>
<td>19.5</td>
<td>1.13 (0.71-1.71)</td>
</tr>
<tr>
<td>≥15</td>
<td>45</td>
<td>33.6</td>
<td>1.34 (0.98-1.79)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves’ hyperthyroidism</td>
<td>25 391</td>
<td>85</td>
<td>63.2</td>
</tr>
<tr>
<td>Toxic nodular goitre</td>
<td>16 331</td>
<td>44</td>
<td>41.3</td>
</tr>
<tr>
<td>Toxic nodular goitre with Graves’ hyperthyroidism</td>
<td>1 911</td>
<td>5</td>
<td>3.8</td>
</tr>
</tbody>
</table>
7 DISCUSSION

This thesis concerns the incidence of hyperthyroidism, the long-term quality of life of patients treated in different ways for this disease. In addition, the suicide risk among these patients has been investigated. All these aspects are important, as hyperthyroidism is a common disease with a substantial effect on the patients’ lives, first in the active phase of the disease and later during the recovery period. The disease will therefore have an impact on the patients’ long-term social life and ability to work and will entail high costs for the society. These studies will be discussed in detail in the following.

The Incidence

The incidence of hyperthyroidism in Sweden is unknown and has not been studied previously. In the clinical situation and in research we usually refer to studies performed in Malmö, and to a study from the inland area of northern Sweden,\textsuperscript{9,11} where the incidence has been calculated to lie between 28.8 and 43 per 100 000 per year. It was therefore considered important in the present investigation to determine total and age-specific incidence of hyperthyroidism and the incidence rates of the subgroups (Graves’ disease, toxic multinodular goitre and solitary toxic adenoma) in the county of Stockholm, in order to extend the coverage of the investigated areas in Sweden. In study I the incidence of hyperthyroidism in adults in Stockholm was calculated to be 32.7 per 100 000 per year.

There is no existing register in which all patients with newly diagnosed hyperthyroidism are registered, which allow us to calculate the incidence. We could have used the nationwide Inpatients Register, but most of the medically and radioiodine-treated patients are not entered in this register, as they are not usually hospitalised during their treatment. Only the surgically treated patients are registered there. This study was therefore performed by using a self-constructed questionnaire that was filled in by the hospital specialists when they diagnosed a patient who had developed hyperthyroidism for the first time. The county of Stockholm is a large area with eight specialised main hospitals/units in which patients with hyperthyroidism are diagnosed and treated. To be certain that as few patients as possible were not registered, 1) the questionnaire was circulated among the hospital specialists before the study was initiated, 2) we have analysed lists of all patients with a diagnosis code for hyperthyroidism and thyrotoxicosis who visited the participating hospitals during the period 2002-2006, and 3) a letter was sent to
all primary health care centres asking them to report if they had treated any patients with hyperthyroidism without referring them to the participating centres during this period. No additional cases were reported from the primary health care centres. In consideration of these measures we are confident that the reported incidence figure is close to the true value. Moreover, the incidence found is comparable to that observed in other studies outside of Sweden, conducted in Iceland, Denmark, the United Kingdom and New Zealand, where it has varied between 23 and 93/100 000/year.8,12-14,113,114

It is well known that factors such as iodine status, age, gender, smoking habits, stress and family history may influence the development of hyperthyroidism and lead to differences in incidence figures from various reports.

The causes of hyperthyroidism are influenced by the endemic iodine exposure. In general it is thought that in areas with a low iodine intake, the incidence of hyperthyroidism is higher than in areas with a high iodine intake, as a suboptimal iodine level induces nodular goitre, and by the time the nodules have become autonomic, hyperthyroidism will developed.115 For comparison, it may be noted that Graves’ disease has been shown to be more common among new cases of hyperthyroidism in Iceland, where the iodine intake is high to normal (300 μg/day), whereas multinodular or uninodular goitre constitutes over half of the new cases in a low iodine intake (40-70 μg/day) area such as Jutland in Denmark.8,116 Another aspect of the endemic iodine status is the change in prevalence of thyroid diseases created by iodine supplementation when general iodination programmes are started in iodine deficient-areas. In this situation some individuals with a latent Graves’ hyperthyroidism may progress to hyperthyroidism. Also, in some patients with non-toxic or autonomous nodular goitre this may progress to a toxic state.14, 117-120 It is therefore important to consider the iodine status in Sweden in relation to the findings in study I. In Sweden endemic goitre was present in many regions at the beginning of the 20 th century. With the introduction of table salt iodisation in 1936 (10 mg/kg), endemic goitre became less frequent. In 1966 the table salt iodization was increased from 10 to 50 mg/kg as some areas still had a high incidence of goitre. The Swedish iodine supplementation programme has thus been implicated for more than four decades and a recent national survey of iodine intake (unpublished) indicates that in Sweden, including Stockholm, the iodine intake generally is sufficient. We therefore consider that the incidence rates of hyperthyroidism found in the present study were observed during a stable and sufficient iodine intake situation.
Graves’ disease accounted for 75 % of the total number of hyperthyroidism cases in the present study I, while TMNG and STA showed a lower incidence. This is in accordance with other reports where it is concluded that the incidence rates of the subtypes are dependent on regional factors.13, 121

The subgroups TMNG and STA were more common among the older age groups, as anticipated. The age-specific incidence of GD was, as expected, highest among the younger patients and decreased with age. As GD is more common among females, the incidence may be influenced by the menopause and the associated changes in hormonal levels. This has been reported for other types of autoimmune diseases such as rheumatoid arthritis, which also shows a decreasing incidence in older patients.122 The total female: male ratio was also in accordance with the ratios found in previous studies (female: male 5.6:1—6.6:1).10, 123

It is suggested that genetic factors have an impact on the development of autoimmune thyroid disease in twins, but knowledge of the specific genes involved is still not complete124.

In general the incidence of hyperthyroidism seems to be increasing according to different reports. The increase may be due to iodine supplementation in previously iodine-sufficient areas125 and in iodine-deficiency areas.126, 127 Further possible reasons for the observed increase may be earlier diagnosis of the disease and more efficient diagnostic tools.11, 128

Quality of life and suicide

There are three treatment modalities for hyperthyroidism, namely antithyroid drugs, surgery and radioiodine. The recommendations for treatment vary between and within different countries. The benefits, side effects and costs60, 61, 129 have been described in various reports from all around the world.50, 51, 61, 64, 130-133 There are a few reports concerning the long-term outcome of the treatments and the associated quality of life of the patients.63, 103, 104, 134 More reports have been published about treatment and QoL modalities that involving Graves’ ophthalmopathy.135-140 The three different treatment modalities have all resulted in a good medical outcome and have been well developed and are all as well accepted by the patients. Although the concept of QoL was introduced into medicine during the mid-1960s,141 no long-term studies on QoL have been conducted on patients with Graves’ hyperthyroidism. The disease often runs a more or less chronic course unless sufficiently treated. The benefits of the treatments in a long-term perspective have not been sufficiently investigated and information of impact of Graves’
hyperthyroidism on the long-term QoL in association with the different treatments is also incomplete. The QoL aspect is even more important for this patient category since these patients may have psychological disturbances that may affect their family and working life.\textsuperscript{142}

During the design period of studies II and III we were interested in finding an appropriate questionnaire that could reveal clinically important changes in QoL over time in Graves’ hyperthyroidism. The time period of these studies, was however 14-21 years. A disease-specific quality of life questionnaire is often more appropriate than a general QoL questionnaire, as the disease-specific instruments focus on aspects of QoL relevant to the disease.\textsuperscript{143-145}

There are six different disease-specific questionnaires for thyroid disease and TAO (see section on QoL and suicide in this thesis) that could have been used for these studies, but they lack documented relevant QoL issues and none of them except GO-QOL\textsuperscript{88} have been validated. Validated disease-specific questionnaires for Graves’ disease are unfortunately lacking.\textsuperscript{93,146} The only questionnaire that is specific for hyperthyroidism is the Hyperthyroidism Complaint Questionnaire. The HCQ, constructed by Fahrenfort et al. (2002), might at first glance have seemed appropriate for our studies, but it has never been properly validated and has not been translated into the Swedish language. Another purpose of these studies was to compare our patients’ scores of QoL with normal values for a general Swedish adult reference population. The questionnaire that we used was therefore the “Medical Outcome Study 36-item short Form health Status survey” (SF-36). In addition, we used the treatment-related QoL2004 modified by our group which we had used in the previous three year follow up.\textsuperscript{61} The main findings in these studies (II and III) were that the hyperthyroidism had long-term negative influence with regard to mental performance and vitality compared with a normal Swedish population. There were no differences among the three different treatment groups regarding QoL that could be related to the mode of treatment of Graves’ hyperthyroidism. It has also been known for a long time that patients with Graves’ hyperthyroidism may exhibit neuropsychiatric changes resulting in agitation, anxiety, emotional lability and even coma,\textsuperscript{147} that can affect the patient’s family and his or her ability to work. In our studies we showed that the mental quality of life could still be decreased even 14-21 years after the treatment. Some caution is appropriate when interpreting our results. The SF–36 may not be have been the most optimal questionnaire for our studies as it is a general questionnaire comprising questions that are meant to estimate general physical and mental health-related QoL. Furthermore, comparison with results obtained from patients who have had another chronic
disease could be useful in order to answer the question of whether our results are related to long-term effects of Graves’ disease in particular or to the fact of having a chronic disease as such.

When the results of the QoL questionnaires (SF-36 and QoL2004) were related to thyroid hormone levels (study III), no associations were found with serum TSH or free $T_4$. However, a low serum-$fT_3$ was correlated to lower General Health Scores in the SF-36 questionnaire. In the QoL2004, questions were included as to whether the patient have other autoimmune diseases, such as diabetes mellitus, pernicious anaemia, alopecia, myasthenia gravis, or primary adrenal insufficiency which is also part of the autoimmune polyglandular syndrome type 2 (APS-2). APS-2 is not a common disease but it may have life-threatening consequences when the diagnosis is overlooked. It was therefore of great interest to include these questions about APS-2 in the questionnaire. There was no occurrence of this disease among our patients. The annual incidence of APS-2 is 1-5 per 100 000, and the absence of patients with APS-2 might be due to the small number of patients in the study, and no conclusions can be drawn regarding the co-occurrence of these diseases. Although a large proportion of the patients had a suppressed TSH (0.02 mU/l), the thyroid hormonal status was not reflected by the QoL instruments. The instruments used may not have been sensitive enough to measure the effects of thyroid disease.

During the work, in studies II and III we discovered that two patients out of a total of 179 had committed suicide. A pilot investigation performed by the National Board of Health and Welfare confirmed the indications of an elevated suicide rate among patients who have been treated for hyperthyroidism. Study IV was therefore conducted to address the question whether patients with a history of hyperthyroidism, especially Graves’ hyperthyroidism, have a higher risk of suicide compared with the general reference population. The study was designed as a retrospective cohort study. This allowed us to analyse a large cohort of patients who had been diagnosed with hyperthyroidism due to Graves’ disease or toxic uni- or multinodular goitre and treated with surgery or radioiodine. Before starting a discussion on this study and its results it is worth considering some epidemiological aspects of great interest in this context.

There are two main types of epidemiological studies, namely the experimental and the observational. The observational studies are mainly cohort and case-control studies. The case-control study is when the cases (individuals with the disease or condition under study) are
compared with controls (individuals who are disease-free). The controls should come from the same source population as the cases and be sampled independently of exposure status. This study design is usable in diseases with a low incidence or prevalence. Studies of this type can be either retrospective or prospective. The information on exposures is usually obtained retrospectively. The cohort study is defined as a study in which a group of individuals with a known exposure are followed up over time, and at the end of the follow-up period the occurrence of the disease is assessed. In this type of study the incidence of a disease can be determined and effects of rare risk factors can be estimated. Cohort studies are more costly than case control studies. Like A case-control studies, A Cohort studies can also be either retrospective or prospective. In study IV we used the cohort study design.

In epidemiology two types of errors are possible - systematic error and random error. A systematic error, often referred to as bias, affects the validity of the results. The systematic error can further be classified into selection bias, information bias and confounding. Selection bias: This originates from the procedures used to select study participants. Selection bias is present when the association between exposure and outcome differs for those who participate compared with those who do not participate in the study. The risk of this bias can occur in both case-control and cohort studies. Information bias: Information bias is also called misclassification and refers to errors in the information collected about the study variables. The effect of misclassification of exposure or outcome depends on whether the misclassification is differential or non-differential. Non-differential misclassification, when the same degree of bias occurs in the comparison groups, only leads to dilution of the effect observed. In differential misclassification the bias differs between cases and controls and is more problematic, resulting in exaggeration and/or underestimation of an effect.

Confounding: Confounding is often defined as confusion or mixing of effects of the exposure under study and other factors. A confounder is a variable that is associated both with the outcome (disease under study, as a cause and not as an effect of this) and with the studied exposure, and is not part of the causal pathway between the exposure and the outcome (E \rightarrow X \rightarrow D). Random error: Random error or chance is a variable of data that we cannot not readily explain. This means differences attributable to chance variation. The error can be minimised by increasing the number of cases and controls in a study. The role of chance can be reflected roughly statistically by the width of the confidence intervals and/or p -values.
Study IV is the first study where disease of hyperthyroidism and the correlation to suicide rate is investigated. The total study cohort consisted of 43,633 patients that had been treated previously by radioiodine or surgery for hyperthyroidism due to Graves’ disease or toxic unilobar or multinodular goitre. The observed number of deaths was 134 in the total cohort. The SMR for the hyperthyroidism patients was 1.24 (95% confidence interval, CI 1.04-1.47). When the SMR was calculated only for the subgroup with history of Graves’ hyperthyroidism it was 1.35 (95% CI 1.07-1.66). The patients in the comparison cohort with a history of atoxic nodular goitre showed no increased risk of suicide (SMR = of 0.92 (95% CI 0.75-1.11).

The results of this study are very interesting but should be interpreted with some caution. A possibility of selection bias concerning the psychiatric status among the patients with previous Graves’ hyperthyroidism is important to keep in mind. Is the increased risk of suicide due to the psychological impact that occurs in patients with hyperthyroidism? Or is it due to the presence of the chronic disease in itself? The correlation of hyperthyroidism, psychiatric disease and suicide can be considered from different aspects. First, is it the condition of hyperthyroidism that induces the psychiatric disease that leads to suicide? Second, is there a pre-existing psychiatric disease that might be a risk factor for developing hyperthyroidism? Third, is it possible that patients with psychiatric disease receiving hospital care are more likely to be diagnosed with hyperthyroidism? The current study design is not sufficient to answer these new questions that have arisen from our results. Further studies are needed to for clarification of these issues.

**Future plans**

In study I we reported the total and age-specific incidence of hyperthyroidism and the incidence rates of the subgroups. In the questionnaire there were questions various parameters (see appendix), such as ethnic origin, smoking habits, endocrine ophthalmopathy, laboratory tests of current hormonal levels, and the type of treatment chosen for the specific subtype. In future studies it would be interesting to determine whether the sub groups of hyperthyroidism are correlated to any particular ethnic origin, and to investigate in more detail the tobacco habits in relation to hyperthyroidism and the occurrence of ophthalmopathy, which have been linked in previous studies. The blood samples for laboratory hormonal tests are important since they were drawn before the patients had their treatments and can be used for genetical and microbiological investigations.
DISCUSSION

It would also be interesting to continue to follow up the patients from studies II and III who were randomised to the three treatment modalities. A thirty-year follow-up could be made and perhaps a more specific disease questionnaire would be available at that time for such a study. As a further aid in the evaluation of the patients’ QoL, patients with another chronic disease that is comparable in severity with hyperthyroidism should then be used as an extra study group. This would allow us to differentiate between QoL issues that are general for chronic disease states and those that are specific for hyperthyroidism patients. This would also allow us to further investigate the risk of suicide among hyperthyroidism patients.
Aims are repeated together with the conclusions for the reader’s convenience.

to determine the total and age-specific incidence of hyperthyroidism and to identify the subgroups of hyperthyroidism (Graves’ disease, toxic uni- or multinodular goitre) in the county of Stockholm (Paper I).

The total, age-specific incidence of hyperthyroidism and the incidence of the subgroups of hyperthyroidism in the county of Stockholm, Sweden were determined.

to determine whether there are any long-term differences in quality of life and state of health in patients treated differently for Graves’ hyperthyroidism and compared with a healthy reference population (Paper II).

A history of Graves’ disease has a negative influence on the mental aspects of quality of life and vitality compared with a reference population. No differences in quality of life were found between the three modes of treatments of Graves’ hyperthyroidism.

to determine whether the quality of life scores in SF36 and QoL2004 in Graves’ hyperthyroidism patients may have been influenced by the current thyroid hormonal status or the level of L-thyroxine (T4) substitution (Paper III).

In patients previously treated for Graves’ hyperthyroidism the quality of life is not influenced by the thyroid hormone status at the time they answered the questionnaire.

to investigate the risk of suicide among patients with hyperthyroidism compared with a general Swedish age- and sex matched population (Paper IV).

An increased risk of suicide was found among patients with a history of hyperthyroidism due to Graves’ disease.

**Studierna i denna avhandling innefattar:**

**Studie I: Incidence of Hyperthyroidism in Stockholm, Sweden, 2003 to 2005**


Via en enkät (se appendix) kunde specialistläkare som träffade patienterna som nyligen insjuknat i hypertyreos registra dem efter deras medgivande till att delta i studien. Under denna period på 3 år diagnostiserades sammanlagt 1431 nya patienter i Stockholms län, dessa var 18 år eller äldre. Detta ger en incidens på 32,7 per 100 000 per år. Även ålder, kön, fördelning i de olika undergrupperna räknades ut.
Studie II: Graves' Disease: A Long-Term Quality-of-Life Follow Up of Patients Randomized to Treatment with Antithyroid Drugs, Radioiodine, or Surgery.

Studie III: Thyroid hormone state and quality of life at long-term follow-up after randomized treatment of Graves' disease.


Studie IV: Hyperthyroidism and suicide: a population-based study in Sweden

ACKNOWLEDGEMENTS

10 ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all those persons who have helped to make this thesis possible, and especially to:

My two supervisors Göran Wallin and Ove Törring, for guiding me through the web of scientific research.
Göran, for your scientific support and for sharing your excellent knowledge in endocrine surgery. Thank you for introducing me to this field.
Ove, for your deep knowledge in endocrinology and in particular thyroid diseases, and for all your enthusiasm for my work, which I have greatly appreciated.

Bertil Hamberger, senior professor, and Jesper Lagergren, professor, for your valuable support and interest in my research.

Staffan Gröndal, head of the Department of Surgery at Danderyd Hospital, for your encouraging support and positive attitude towards my work.

My co-authors Gun Jörneskog, Stefan Lönn, Li Yin, Olof Nyrén, Owe Tullgren, Per Hall, Bertil Hamberger, Göran Lundell, Leif Tallstedt, Frank Träisk, Jan Calissendorff, Mikael Lantz, Bengt Hallengren, Hans Ohrling, Martin Bäckdahl, at Karolinska Institutet, Peter Laurberg at Aarhus University Hospital, Denmark and Peter Nilsson, Roland Sjöberg, and Cecilia Laurell at Royal Institute of Technology, for your valuable contributions and good collaboration.

Erik Näslund, professor, for arranging my working schedule so as to allow me to focus on my thesis.

All the staff at the Department of Molecular Medicine and Surgery for your contributions in many ways.

My colleagues and friends at the Department of Surgery at Karolinska University Hospital, Norrtälje Hospital and Danderyd Hospital.

Inkeri Schultz and Magnus Larsson, my clinical supervisors during my surgical training, for excellent good advice and support.

My room mates Anna Brodin, Karin Westberg and Silja Karlgren at Danderyd Hospital for laughs and all our conversations about life.

Evangelos Chandanos, who finished his thesis four months before me, thank you for all your tips on how to get through the administrative jungle. My room mates at Karolinska University Hospital, especially Catharina Ihre-Lundgren, for her help in reading through part of my thesis.
ACKNOWLEDGEMENTS

All my friends, especially Åsa, Sara, Pia, Susanna and Johan, I have enjoyed sharing our
great moments together and also all the jogging and mountain biking. Special thanks to Åsa for
fun at camping and kayaking.

Birgitta and Ulf Nordling, my parents-in-law, for all your support.

My parents Alice and the late Jacob and my brothers and sisters, Nidal, Hilda, Isak, Ninos
and Maria for all your care and for always believing in me.

My father, you passed away shortly before I had come to the end of this thesis. You taught me
how to set a goal and work hard for it. Even though it was a hard and sad time at the end, now
it is finished. This thesis is dedicated to you.
I miss you so much.

Erik, my love and my best friend. Thank you for your patience, all your care and for your
encouragement in my clinical and scientific work. Our lovely daughter Lea who is always
reminding me about the meaning of life. I love you.
REFERENCES

11 REFERENCES


REFERENCES


39. Haik JDaB. Thyroid Eye Disease: Diagnosis and Treatment: Hardcover; 2002.


REFERENCES


REFERENCES


REFERENCES


REFERENCES


12 APPENDIX

12.1 THE INCIDENCE FORM

12.2 QOL-2004

12.3 SF-36
Registrering av nyinsjuknade patienter med tyreotoxikos, år 2003-5


Namn:..................................................................................................Pat inform: 1 Ja, 2 Nej

Etnisk bakgrund: 1. Född i Sverige 2. Född i Europa, ej Sverige 3. Född utom Europa

Antal år i Sverige (grupp 2,3) före insjuknandet............

Datum för diagnos av tyreotoxikos (ååmmdd):

Typ av tyreotoxikos:  1. Graves sjd (GD)  2. Toxisk multinodös struma (TMNG)  3. Solitärt toxiskt adenom (STA)

Amiodaronbehandlad inom de senaste 12 månaderna: 1. Nej   2. Ja


Klin bedömning


Lab:  

T3..............fritt T3.......... 

T4..............fritt T4.......... 

TSH.............TRAK......(refomr............).TPO-ak...........(refomr............)

Tyreoideascintigrafi:  1. Nej  2. Ja

Spårjodundersökning:  1. Nej  2. Ja

Planerad huvudbehandling:  1. Tyreostatika  2. Radiojod

3. Operation  4. Expektans/Betablockad  5. Övrigt

Ev kommentar till terapi:

Sjukhus/Klinik:............................................... Rapportör:.............................................................

Kommentarer:........................................................................................................

Ifylld blankett skickas till:
Mirna Nordling/Göran Wallin
Kirurgmottagningen Karolinska sjukhuset
171 76 Stockholm
QoL — 2004

Please answer these questions starting three years after your first treatment:

A

1. Have you after the treatment had a relapse of increased metabolism?: Yes □ No □ Don’t know □
   If yes, which year? __________
2. Have you had or have a low metabolism?: Yes □ No □ Don’t know □
   If yes, which year did it start? __________
3. Did you have any eye problems during this period?: Yes □ No □ Don’t know □
   If yes, which year did it start? __________
   If yes, are your eye problems currently: Worse □ Better □ Unchanged □
4. Are you using thyroid hormones? If yes, what brand and what is the daily dose?: _________________________________

B

1. Do you have diabetes mellitus? Yes □ No □
2. Do you have anaemia because of vitamin B12 deficiency (pernicious anemia) that makes you have to take vitamin B12 supplement?: Yes □ No □
3. Do you experience hair-loss in patches?: Yes □ No □; Total hair-loss?: Yes □ No □
4. Do you have the neuromuscular disease, myasthenia gravis?: Yes □ No □
5. Do you have adrenal disorder with cortisol deficiency, Addison’s disease?: Yes □ No □
6. Have you been examined for osteoporosis?: Yes □ No □
   If yes, do you have osteoporosis Yes □ No □
   In which hospital did you do the examination? _______________________________
   Have you had any fractures?:
   Ribs □ Femur/hip □ Arm □ other places □
   Have you received treatment for osteoporosis?: Yes □ No □
7. Do you have heart disease?: Yes □ No □
   If yes, what type of disease and treatment: _________________________________
   Heart fibrillation □ Heart infarct □ Other heart disease □
8. Have you experienced memory problems that made you contact a physician?: Yes □ No □
9. Have you experienced concentration difficulties that made you contact a physician?: Yes □ No □
10. Do you have any other diseases? _________________________________

C

Do you judge that your disease has:

1. Affected your career/work? Yes □ No □ Don’t know □
   If yes, has it affected you: Positively □ Negatively □
   If yes, for 5 years □ 10 years □ 15 years □ Other □ __________
2. Affected your social possibilities/private life? Yes □ No □ Don’t know □
   If yes, has it affected you: Positively □ Negatively □
   If yes, for 5 years □ 10 years □ 15 years □ Other □ __________
3. Affected your relation to your family? Yes □ No □ Don’t know □
   If yes, has it affected you: Positively □ Negatively □
   If yes, for 5 years □ 10 years □ 15 years □ Other □ __________
4. Caused a physical hindrance? Yes □ No □ Don’t know □
   If yes, for 5 years □ 10 years □ 15 years □ Other □ __________
5. Affected your spare time occupation? Yes □ No □ Don’t know □
   If yes, has it affected you: Positively □ Negatively □
6. Made you feel gloomy and sad? Yes □ No □ Don’t know □
   If yes, for 5 years □ 10 years □ 15 years □ Other □ __________
7. Made you feel worn-out? Yes □ No □ Don’t know □
   If yes, for 5 years □ 10 years □ 15 years □ Other □ __________
8. Made you feel tired? Yes □ No □ Don’t know □
   If yes, for 5 years □ 10 years □ 15 years □ Other □ __________
9. Other positive or negative findings or experiences that you hold the disease responsible for? _________________________________
10. Do you feel well now? Yes □ No □ Don’t know □
SF-36(tm) Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Patient Name: _________________________________________________________________________________
SSN#: ________________________________________       Date: _______________________________________
Person helping to complete this form: ________________________________________________________________

1. In general, would you say your health is:
   - Excellent
   - Very good
   - Good
   - Fair
   - Poor

2. Compared to one year ago, how would you rate your health in general now?
   - Much better now than a year ago
   - Somewhat better now than a year ago
   - About the same as one year ago
   - Somewhat worse now than one year ago
   - Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
   a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
      - Yes, limited a lot.
      - Yes, limited a little.
      - No, not limited at all.
   b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?
      - Yes, limited a lot.
      - Yes, limited a little.
      - No, not limited at all.
   c. Lifting or carrying groceries.
      - Yes, limited a lot.
      - Yes, limited a little.
      - No, not limited at all.
   d. Climbing several flights of stairs.
      - Yes, limited a lot.
      - Yes, limited a little.
      - No, not limited at all.
   e. Climbing one flight of stairs.
      - Yes, limited a lot.
      - Yes, limited a little.
      - No, not limited at all.
   f. Bending, kneeling or stooping.
      - Yes, limited a lot.
      - Yes, limited a little.
      - No, not limited at all.
g. Walking more than one mile.
   - Yes, limited a lot.
   - Yes, limited a little.
   - No, not limited at all.

h. Walking several blocks.
   - Yes, limited a lot.
   - Yes, limited a little.
   - No, not limited at all.

i. Walking one block.
   - Yes, limited a lot.
   - Yes, limited a little.
   - No, not limited at all.

j. Bathing or dressing yourself.
   - Yes, limited a lot.
   - Yes, limited a little.
   - No, not limited at all.

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
   a. Cut down the amount of time you spent on work or other activities?
      - Yes
      - No
   b. Accomplished less than you would like?
      - Yes
      - No
   c. Were limited in the kind of work or other activities?
      - Yes
      - No
   d. Had difficulty performing the work or other activities (for example, it took extra time)
      - Yes
      - No

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
   a. Cut down the amount of time you spent on work or other activities?
      - Yes
      - No
   b. Accomplished less than you would like?
      - Yes
      - No
   c. Didn’t do work or other activities as carefully as usual?
      - Yes
      - No

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
   - Not at all
   - Slightly
   - Moderately
   - Quite a bit
   - Extremely

7. How much bodily pain have you had during the past 4 weeks?
   - Not at all
   - Slightly
   - Moderately
   - Quite a bit
   - Extremely
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

a. did you feel full of pep?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time

b. have you been a very nervous person?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time

c. have you felt so down in the dumps nothing could cheer you up?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time

d. have you felt calm and peaceful?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time

e. did you have a lot of energy?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time

f. have you felt downhearted and blue?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time
g. did you feel worn out?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time

h. have you been a happy person?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time

i. did you feel tired?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - None of the time

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?
   - All of the time
   - Most of the time
   - Some of the time
   - A little of the time
   - None of the time

11. How TRUE or FALSE is each of the following statements for you?

   a. I seem to get sick a little easier than other people
      - Definitely true
      - Mostly true
      - Don't know
      - Mostly false
      - Definitely false

   b. I am as healthy as anybody I know
      - Definitely true
      - Mostly true
      - Don't know
      - Mostly false
      - Definitely false

   c. I expect my health to get worse
      - Definitely true
      - Mostly true
      - Don't know
      - Mostly false
      - Definitely false

   d. My health is excellent
      - Definitely true
      - Mostly true
      - Don't know
      - Mostly false
      - Definitely false