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UNIVERSITY OF COPENHAGEN

PhD thesis

Mette Andersen Nexø

Work Disability among People with Benign Thyroid Diseases in Denmark

NATIONAL RESEARCH CENTRE
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Author:	Mette Andersen Nexø
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Academic advisors:	Principal supervisor: Professor Jakob Bue Bjørner Co-supervisor: Senior researcher, Torquil Watt Co-supervisor: Professor Erik Lykke Mortensen
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Assessment committee:	Professor Finn Diderichsen (chairman) Associate Professor Thomas H. Brix Professor Ute Bültmann

Preface

Before I started this thesis, I was familiar with the term thyroid disease from the time I had worked as a clinical psychologist at a psychiatric ward. However, I had never talked to anyone about their thyroid disease. During my work with thyroid diseases, I was amazed to learn how little attention thyroid diseases have received in the public sphere despite their prevalence in the general population. I was also amazed to learn that people I had known for years had never found it relevant to tell me that they had a thyroid disease until they learned about my research project. I gained the impression that thyroid diseases were hidden diseases, diseases that would only be noticeable if people with the disease claimed its existence. One of the advantages of having a chronic disease that is hidden from others is avoiding the, perhaps unnecessary, assignment of a sickness role, as Parsons pointed out decades ago (Parsons 1951). However, the main disadvantage is the lack of recognition and necessary support if the thyroid disease has a significant impact on work and daily life. I hope this thesis - by scientifically clarifying the possible impact of thyroid diseases on work ability – can benefit the many people living with a thyroid disease. Also, I hope that this thesis can be helpful to the many health care professionals and other professionals who work with people with thyroid diseases.

Many people contacted me throughout the course of this thesis to volunteer as participants in the research projects or to express their interest and support for the project. Some of these people told me about how their thyroid disease had affected their work life. Some had never experienced symptoms that had a significant impact on their daily lives or they had overcome symptoms that once affected their work lives. Others experienced symptoms continuously, but were mostly able to compensate for them during their work days. Yet again, others were deeply affected by their symptoms, experiencing long periods of unemployment or sickness absence

fearing the financial insecurity and social consequences of not being able work. I want to thank all those who contacted me for bringing attention to the relevance of the topic and for bringing me these insights. Also, I want to thank all the people who participated in the research projects, whether in interviews conducted for the qualitative study, in interviews testing the questionnaire, by responding to the questionnaire or by letting me sit in during medical consultations.

This thesis was a result of a research collaboration between The National Research Center for the Working Environment, Odense University Hospital, and Copenhagen University Hospital (Rigshospitalet). It was funded by the Danish Council for Strategic Research. Three different research projects comprise the thesis. These research projects would never have been executed in due time without skilled assistance from the staff at these three institutions. The different teams have provided excellent data management, practical help and social support throughout the course of this thesis.

Moreover, these projects would not have been successful without the great dedication of all the research collaborators. Special thanks are extended to Ulla Feldt-Rasmussen and Åse Krogh Rasmussen from the Department of Medical Endocrinology, Rigshospitalet, and to Laszlo Hegedüs and Steen Bonnema at the Department of Endocrinology and Metabolism, Odense University Hospital, for opening my eyes to the medical world of endocrinology and for being open to other research paradigms that are rarely applied within the field of endocrinology. Also, special thanks are given to Stine Birk Nissen, Per Cramon, Christian Winther and Mogens Grønvold.

I also deeply appreciate the support from my supervisors, Erik Lykke Mortensen and Bryan Cleal for being there if needed. Special thanks are extended to my project supervisor, Torquil Watt, for laying the foundations for this thesis and for providing excellent guidance and support. Also, special thanks are given to my principal supervisor, Jakob Bue Bjørner, for always keeping calm and exhibiting intellectual clarity and for his great dedication to orchestrate solutions to the many different challenges faced during the course of this Ph.D.

Thank you to all my great colleagues for the professional and social support and, more importantly, making the many hours spent in the office fun. I thank the National Research Center for the Working Environment and my leader Elsa Bach for guidance and support in the management of the many projects. Thanks to the Section of Social Medicine, Department of Public Health, Copenhagen University, for opening the doors to a caring, passionate and dedicated research environment.

Finally, the completion of this research project would not have been possible without the great support from my husband and my mother and father. Thank you for taking good care of the girls during the many hours spent in the office.

Contents

1. Introduction

Roughly 15 % of the adult Western population suffers from some form of thyroid disease (Canaris GJ et al. 2000; Carlé A et al. 2006; Vanderpump MPJ & Tunbridge WMG 1996). Many of the thyroid diseases involving thyroid dysfunction are diagnosed in early adulthood and have a chronic course. Thyroid dysfunction has a significant impact on somatic and psychiatric morbidity (Brandt et al. 2013b; Brandt et al. 2013c; Thvilum et al. 2013a; Thvilum et al. 2014), and both short- and long-term health-related quality of life is impacted by a number of thyroid diseases (Elberling et al. 2004; Fahrenfort et al. 2000; Kahaly et al. 2002; Kahaly et al. 2005; Ponto & Kahaly 2012; Saravanan et al. 2002; Terwee et al. 2002; Watt T et al. 2006). Although thyroid diseases are prevalent in the work force, the impact of thyroid disease on work function has received little attention.

This thesis examines work disability among people with thyroid diseases, with the overall aim of evaluating whether work ability is impacted by benign thyroid diseases. This aim was examined in three studies: A register-based cohort study, a qualitative interview study, and a survey. Each of these studies is reported as research papers enclosed in appendix 1. Because the background of each study is already described in the papers, the purpose of this introduction is to outline the main theoretical and empirical perspectives of relevance to work disability among people with thyroid diseases.

Health-related disability and work ability can be researched from different perspectives involving many disciplines. Therefore the introduction will begin with outlining the societal perspectives of work disability, followed by a clarification of the biomedical understanding and prognosis of thyroid diseases. Then the patient-oriented perspective will be outlined, including quality of life and the psychosocial aspects of having a thyroid disease. Finally, these perspectives will be combined in a theoretical model that is used to explain how work disability can develop in thyroid diseases.

1.1. Societal perspectives on disability from chronic diseases

Recent years have witnessed increased interest in health-related disability from chronic diseases. An ageing work force challenges most Western countries because of longer life expectancies and lower birth rates. Because older populations have higher risks of developing disabilities, the

number of people with disabilities is growing (Prins 2013). This risk of disability is mostly driven by the rise in incidence of chronic diseases - often labeled the global burden of disease (Murray et al. 2012; World Health Organization 2009) - increasing the number of people with lifelong disabilities.

Lifelong health-related disabilities have great individual and socioeconomic consequences. Sickness absence, unemployment or a low level of participation in the labor market is common for people with disabilities in Europe (Eurofund 2004; OECD 2010), including Denmark (The Nordic Council of Ministers 2004). Chronic diseases can increase the risk of labor market exclusion through sickness absence, unemployment or early retirement, or it can increase difficulties participating in employment because of difficulties returning to work. Difficulties retaining work have a great impact on the financial security, identity and well-being of people with disabilities (Coutu et al. 2013). Also, a low degree of employment can increase the risk of poverty and social exclusion, which may in turn have adverse health effects (Holland et al. 2011). The employer may fear economic consequences related to employing workers at risk of absenteeism or decreased productivity while at work (Johns 2010). A shared goal among society, employers and people with chronic diseases may be to retain the possibility of employment.

The gloomy prospect of a work force including an ever smaller proportion of the population has caused major concerns on a societal level. This has called for new strategies to prevent the exclusion of people with disabilities from the labor market and include people with disabilities in the labor force (Eurofund 2004; Eurofund 2012). However, to develop effective preventive or rehabilitation strategies, careful consideration must be given to potential conflicting economic and health-related goals, e.g., a strategy solely prioritizing economic aspects might have adverse health consequences for the person suffering from the disease. Making a theoretical distinction between work ability and labor market exclusion is important in this regard, as some people might be able to retain the link to work, despite of a decreased capacity to work. With regard to thyroid diseases, the first step is to examine how the work function can be impacted. Therefore a biomedical understanding of thyroid diseases is provided. Subsequently, it will be outlined whether the existent literature document that decreased work ability also incurs risks of subsequent labor market exclusion among people with thyroid diseases.

1.2. Thyroid diseases: biomedical underpinnings, symptoms and diagnosis

The thyroid gland is located in the neck, below the laryngeal prominence (Adams apple), and is responsible for the production of thyroid hormones. Thyroid hormones help control the pace of energy use in the body (metabolism). They affect all cells in the body and, thus, physical and mental functioning. Thyroid hormones (triiodinethyronine (T3) and thyroxine (T4) are regulated via inhibiting and releasing pathways. T4 is converted into T3 in peripheral tissues. The release of these hormones is stimulated by a thyroid-stimulating hormone (TSH) produced by the anterior pituitary, which again is regulated by a thyrotrophin-releasing hormone (TRH) produced by the hypothalamus (Figure 1). The thyroid hormones exhibit negative feed-back on the releasing factors, establishing a classical homeostatic system (Santisteban 2005). A normal thyroid function is a requisite for the normal mental and physical development of children, and it involves vital functions in the body, e.g., heart rate, respiration, digestion, heat/cold sensitivity, and emotions (Brown et al. 2005).

A thyroid disease is a medical condition that impairs the structure or function of the thyroid. Thyroid diseases, as classified by the International Classification of Diseases (World Health Organization 2010), involve a wide spectrum of diseases ranging from congenital diseases to drug-induced thyroid abnormalities. They affect more women than men with a seven to one ratio. Although the risk increases with age, thyroid diseases can occur at all ages, and many of these cases are diagnosed in early adult life. The prevalence of thyroid diseases may also differ according to iodine-replete regional area or ethnic groups (Vanderpump & Tunbridge 1996). In this thesis, thyroid diseases refer to six of the main groups of benign thyroid diseases:

1. Non-toxic goiter (diffuse, uni- or multi-nodular non-toxic goiter and thyroid cysts)
2. Toxic nodular goiter (uni- or multi-nodular toxic goiter)
3. Autoimmune hypothyroidism (Hashimoto's thyroiditis)
4. Graves' hyperthyroidism (Graves' disease without orbitopathy)
5. Graves' orbitopathy (thyroid associated opthalmopathy)
6. Other thyroid diseases, e.g., post-partum thyroiditis or de Quervain thyroiditis

1.2.1. Goiters

Goiters are among the most common thyroid diseases and are characterized by an enlarged thyroid gland. Enlarged thyroid gland (goiter) cases have been documented for thousands of years in Ancient China, Egypt, India and Greece (ATA 2014; Lydiatt & Bucher 2011; Sawin

1996). Goiters can be caused by a dietary iodine deficiency (endemic goiter), where the thyroid gland grows in size and may ultimately become overactive. A high prevalence of goiter has been linked to areas of low iodine in water and soil or in populations with low consumption of seafood. Because of the risk of severe developmental impairments in the fetus and in children (cretinism) and the risk of goiters in the adult population most developed countries have secured a sufficient intake of iodine for the general population by fortifying salt with iodine (Delange 1996).

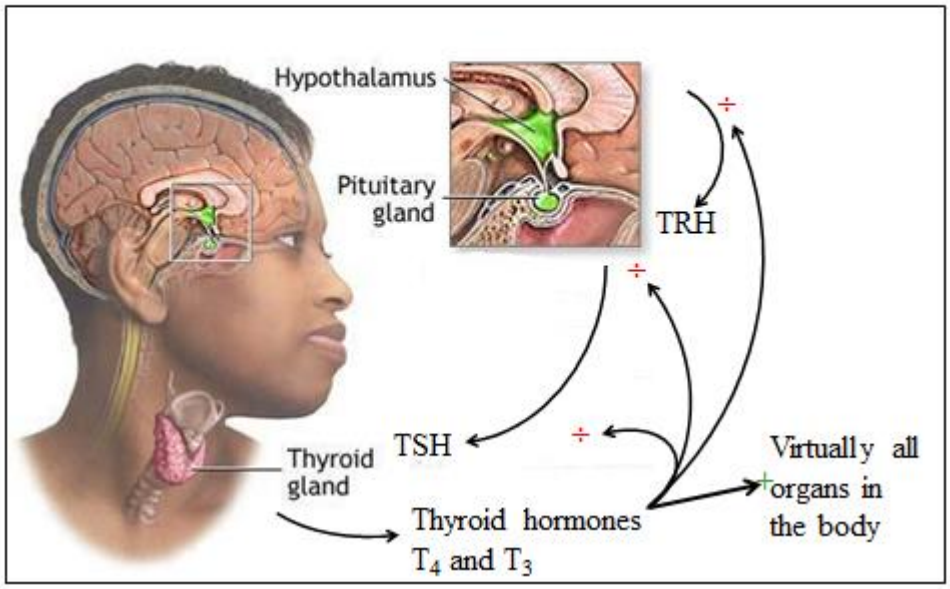
An enlarged thyroid gland, whether uni-nodular, multi-nodular or diffuse, without increased production of thyroid hormones is defined as 'non-toxic' goiter. Depending on the size, compression in the neck, compromised breathing (dyspnea) and cosmetic concerns can be some of the major consequences of having a goiter. Typical goiter symptoms are neck swelling, hoarseness, discomfort swallowing, pain in the throat, or a weaker voice. Apart from a too low iodine intake, a gland can also grow in size as part of a hyper- or hypothyroid state. Toxic nodular goiter refers to functionally autonomous thyroid nodules, which are well-demarcated areas within the gland, with an overproduction of thyroid hormones (Hermus & Huysmans 1996). In classical Hashimoto's thyroiditis, a hypo functioning thyroid gland is enlarged due to infiltration of the thyroid tissue with lymphoid cells.

1.2.2. Autoimmune hypo- and hyperthyroidism with or without orbitopathy

Hypothyroidism is caused by an underactive thyroid gland. The result is the slowing of all metabolic processes causing a wide spectrum of physical and mental symptoms, including fatigue, weight gain, depressive symptoms, dry skin, and cold intolerance (Weetman 1996). By contrast, hyperthyroidism causes the thyroid gland to produce excessive amounts of thyroid hormones, accelerating the metabolism and resulting in symptoms such as irritability, weight loss, increased heart rate, perspiration, and heat intolerance (Davies 1996). Some of the most common causes of hypo- or hyperthyroidism are of autoimmune origin, namely, autoimmune hypothyroidism, or Hashimoto's thyroiditis, and Graves' hyperthyroidism, also called Basedow's disease. Furthermore, the autoimmune reaction responsible for the dysfunction of the thyroid can also target the structures within the orbit, resulting in inflammation, swelling and redness of the eye. These eye complications occur mostly in Graves' hyperthyroidism, a condition referred to as Graves' orbitopathy, previously called thyroid-associated opthalmopathy. Graves' orbitopathy can, in worst case, cause eye complications such as

protrusion of the eyeballs, swelling of the eye surroundings, double vision, and impaired vision (Perros & Dickinson 1996).

Figure 1. Illustration of thyroid function



1.2.3. The diagnosis of thyroid diseases

Goiters are diagnosed by palpation, thyroid ultrasonography, or other relevant imaging. Testing serum levels of TSH, T3 and T4 and of anti-thyroglobulin antibodies (TPO-Ab) and anti-thyroid peroxidase antibodies (TG-Ab) is helpful to establishing the diagnosis. In non-toxic goiters, the hormone levels are within normal reference ranges; in toxic goiter, the hormone levels are above the normal reference range prior to treatment (Hegedus et al. 2009; Hegedus & Bennedbaek 1996). The thyroid gland may also become enlarged as part of an autoimmune process, where the gland becomes infiltrated with leukocytes (white blood cells), usually lymphocytes, accompanied by under-functioning of the thyroid gland (Hashimoto's thyroiditis). According to the diagnostic criteria, low T4 and elevated TSH indicate hypothyroidism. Suppressed TSH and high T4 reveal hyperthyroidism. Autoimmunity is revealed by abnormal levels of thyroid-specific autoantibodies (e.g., TSHR-Ab, TPO-Ab)(Toft & Beckett 1996). Clinical ophthalmological assessments of the presence of ocular signs and symptoms are usually sufficient to diagnose Graves' orbitopathy and to classify the severity of eye complications. The symptoms of hypo- and hyperthyroidism may overlap or change during the course of the disease - often because of changes in clinical conditions after treatment initiation.

1.3. The treatment and prognosis of thyroid diseases

In Denmark, thyroid diseases are treated in primary care by general practitioners or in hospital-based units within the specialized area of endocrinology. Hypothyroidism is often treated in primary care, although in cases of current or prior to planned pregnancy or if requested by the patient, specialized treatment can be offered. The diagnosis of goiters or the complications of Graves' hyperthyroidism often requires specialized examination or treatment and, therefore, often requires specialized care.

1.3.1. Treatment of goiters

Non-toxic goiters usually grow slowly without symptoms, and in many cases no treatment will be necessary. However, if the goiter increases markedly in size, destruction or removal of (parts of) the thyroid gland via surgery or radioactive iodine can be necessary (Hermus & Huysmans 1996). In the latter method, a dose of radioactive iodine is taken orally and reaches the thyroid gland via the bloodstream, destroying the overactive thyroid cells over time. No significant immediate side-effects of this treatment are expected, and therefore, this treatment is often undertaken in an outpatient setting. Within 12-18 months, the thyroid volume is normally reduced considerably in size (Bahn & Castro 2011). The treatment of toxic nodular goiters mainly involves the destruction or removal of (parts of) the thyroid gland by radioactive iodine or surgery, respectively. Sometimes these treatments also result in an underactive thyroid gland requiring treatment of hypothyroidism.

1.3.2. Treatment of autoimmune hypo- and hyperthyroidism

The treatment of autoimmune hypothyroidism requires lifelong hormone replacement therapy. The standard medicament is synthetic levothyroxine (T4), which is taken orally. Blood samples monitoring hormone levels at approximately six-week intervals are required until these levels are stable, and subsequent samples are usually only required once a year. Most individuals respond well to treatment, and the disease usually progresses slowly. However, often the thyroid gland eventually progresses to complete thyroid failure, and therefore adjustments in medicine are often needed over a life course (Weetman 1996).

The treatment of Graves' hyperthyroidism often involves anti-thyroid medication which aims to inhibit the overproduction of thyroid hormones. Medicaments such as propylthiouracil or methimazole are taken for more than one year to maintain normal thyroid function. Beta

blockers may also be used to dampen the effects of thyroid hormones on the body, including anxiety and irregular heartbeats. Sometimes complete recovery can occur, but 50% of the patients relapse within the first two years after treatment initiation. (Davies 1996). If relapse occurs, radioactive iodine therapy or surgery is recommended, although this treatment involves the risk of permanent hypothyroidism. If severely affected by Graves' orbitopathy, treatment may require corticosteroids (e.g., prednisone) or orbital radiotherapy in which targeted x-rays destroy tissue behind the eyes. Orbital decompression surgery is also an option. These treatment options for Graves' orbitopathy are all associated with severe side effects (Bahn et al. 2011; Leo et al. 2012).

1.3.3. Prognosis of thyroid diseases

Compared with most chronic diseases, thyroid diseases are regarded as relatively easy to monitor and treat. Objective biomarkers are used to identify the disease, and the biophysical mechanisms of the thyroid function are well defined enabling restoration of thyroid function. In hypo- and hyperthyroidism, thyroid hormone levels are often restored (within the normal laboratory range) within the first 3-6 months after the onset of illness (Elberling et al. 2004; Hegedus 2009). The course of autoimmune hypothyroidism and Graves' hyperthyroidism varies with age, the duration of the illness, the magnitude of the thyroid dysfunction, the regional area of residence, and the extent of autoimmune responses (Braverman & Utiger 1996; Carle et al. 2013). Hypothyroidism and hyperthyroidism have been linked to increased mortality and morbidity (Brandt et al. 2011; Brandt et al. 2013a; Brandt et al. 2013b; Brandt et al. 2013c; Thvilum et al. 2013a; Thvilum et al. 2013b) with an increased risk of death due to cardiovascular diseases in Graves' disease and an increased risk of developing affective disorders (Brandt et al. 2013b; Thomsen et al. 2005; Thvilum et al. 2014)

1.3.4. Health-related quality of life among people with thyroid diseases

Most patients respond well to treatment, and once the biophysical dysfunction of the thyroid gland has been restored individuals with hypo- and hyperthyroidism have traditionally been regarded as "cured". This assumption is, however, questioned in a number of recent studies that include patient-reported outcomes (PROs). PROs aim to represent the patients' view in clinical settings as a supplement to the biomedical outcomes and are usually obtained from health-related quality of life (HRQOL) questionnaires. The PROs included in thyroid disease studies mainly provide three types of information: self-reported symptoms, experienced limitations to

functioning, and well-being (Fayers & Machin D. 2007). Recently, a thyroid-specific quality of life questionnaire (ThyPRO) was developed to measure self-reported outcomes in benign thyroid diseases (Watt 2007; Watt et al. 2010a). This research, along with other recent studies, documents that most aspects of HRQOL are impaired in the acute phase of thyroid diseases (Watt T et al. 2006). Although treatment leads to improvement in HRQOL, a substantial percentage of patients with thyroid diseases (ranging from 14% to 87%) experience a persistent impact on HRQOL a year after initiation of treatment or after reaching euthyroidism (Bianchi et al. 2004; Coulter et al. 2007; Elberling et al. 2004; Jaeschke et al. 1994; Kahaly et al. 2002; Kahaly et al. 2005; Leo et al. 2012; Ponto & Kahaly 2012; Terwee et al. 2002; Terwee et al. 2001; Watt T et al. 2006; Watt T et al. 2007; Watt et al. 2012).

1.3.5. The psychosocial aspects of living with a thyroid disease

The thyroid diseases studied here vary greatly in their severity, duration, and course. Understanding the biological and psychological processes that affect disability can help identify important factors for rehabilitation and management of the disability. Psychological functioning is one of the main determinants in disease management and HRQOL outcomes (Testa & Simonson 1996), whereas the physical mechanisms responsible for symptoms in thyroid diseases are well understood, the psychological factors affecting the disease and HRQOL outcomes are poorly understood.

The psychosocial aspects of living with and managing chronic diseases have been documented in studies applying mainly qualitative research methodologies (Conrad 1990; Gerhardt 1990). One major contribution stems from the work of Charmaz (Charmaz 1995; Charmaz 1999; Charmaz 2002; Charmaz 2012) who shows that the experiences related to a variety of different chronic diseases all entail a loss of identity, making it difficult to integrate the consequences of living with a chronic illness with the sense of self before the onset of the illness. Another major contribution is the work of Bury (Bury 1991) who described how the emergence of chronic illness can threaten the coherence and meaning in everyday life that previously were taken for granted. It remains unknown whether this is also the case for people with thyroid diseases.

1.3.6. Work disability among people with thyroid diseases

Although being able to work and support your self is an important aspect of quality of life, few studies have looked into the impact of thyroid disease on work ability. In one study, self-

reported outcomes of work role functioning (Role Emotional and Role Physical sub-scales) from the Short Form (SF-36) HRQOL questionnaire were included in a study examining the psychosocial implications of Graves' orbitopathy (Kahaly et al. 2005). People with Graves' orbitopathy showed worse self-reported work role functioning due to physical health or emotional problems compared with German population-based norms. In another study, newly diagnosed people with hypo- or hyperthyroidism and goiter also showed worse work role functioning scores on these SF-36 subscales compared with Italian population-based norms (Bianchi et al. 2004). A few studies have examined exclusion from the labor market regarding returning to work, sickness absence or disability pensioning. Examining the socio-economic consequences among people with Graves' orbitopathy, Ponto et al. (Ponto et al. 2013) showed that 22% were temporarily work disabled and 6% were permanently work disabled. The mean duration of sick leave was 22 days per year against a German average of 12 days per year. Work disability in Graves' orbitopathy was also worse compared to a clinical sample of other thyroid diseases (hyper- or hypothyroidism and benign goiter). Thirty percent of patients with hyperthyroidism were assessed by a clinician to be completely or partially work disabled, hindering them from returning to full time employment (Fahrenfort et al. 2000). However, these findings may be biased due to lack of clear criteria defining work disability. Although these studies suggest that people with thyroid diseases experience work disability that might lead to temporary or permanent labor market exclusion these studies include a short follow-up time and lack proper control for the duration of the disease and comorbidities. Also, self-reported measurements may suffer from information bias if patients under- or over-assess their work ability or they may suffer from selection bias due to patient non-response.

In the US, the social security administration (SSA), which approves disability benefits for health conditions, does not have a specific disability listing (SSA listing) for thyroid disorders. The SSA guidelines assume that most people can control their thyroid disorder with medication and that thyroid disease in itself does not limit normal functioning at work or in daily life. With regards to autoimmune hypothyroidism 'no work restrictions or accommodations' with regard to return to work should be necessary, and sickness absence benefits are estimated to an 'optimum' of seven days (Reed 2005a). People can nevertheless qualify for predefined disability benefits if suffering from comorbid conditions (e.g., heart problems, depression or anxiety). No official guidelines exist within the Danish social security system.

1.4. A conceptual framework for work ability in thyroid diseases

There is no generally agreed definition of the term 'work ability'. The following sections will therefore define the term work ability and how work ability can be measured and it will provide a theoretical framework for the development of work disability in thyroid diseases.

1.4.1. Definition and measurements of work ability

As noted by Tengland (Tengland 2011), work ability is an acquired ability that is defined as the qualities required to perform a given task, either a necessary skill, competence, or the ability to cope with a problem in the context of work. Apart from health factors, a concept of work ability will therefore also depend on individual factors (e.g., the type of job, skill training, education) and environmental factors (e.g., work environmental factors). The widely used measure of work ability, the Work Ability Index (Ilmarinen 2007), is rooted in a strain-stress model which defines work ability as a balance between job demands and personal resources. This definition of work ability is concerned with the assessment of work ability as it currently stands, how it might be in the near future, and how able the individual is to meet the work demands with respect to related health and mental resources (Hasselhorn 2004). Health-related *dis*ability can, in this regard, be understood as limited personal resources, making it more difficult to meet the demands of a job. Although this definition is meaningful in evaluating the here-and-now ability to work, it does not encompass the cause of work disability. Acquired, congenital, or developmental diseases are often the cause of decreased work ability, and identifying the causes can be a useful strategy in preventing and managing work disability.

The term 'work functioning' has been used in the literature to refer to how well a person functions while at work (Nieuwenhuijsen et al. 2010). One dimension deals with the socio-economic consequences of the condition, e.g., self-reported loss of productivity or other costs. Another dimension is the impact on work role functioning of various health factors. The word 'role' refers to the employment role or roles involved in carrying out different tasks in everyday life and thus encompasses the importance of contextual factors. This dimension is often quantified in self-reported questionnaires by generic measurements assessing the overall perception of functioning (e.g., SF-36) or by specific measurements such as limitations in performance, pace, or quality of specific work tasks (Lerner et al. 2001)

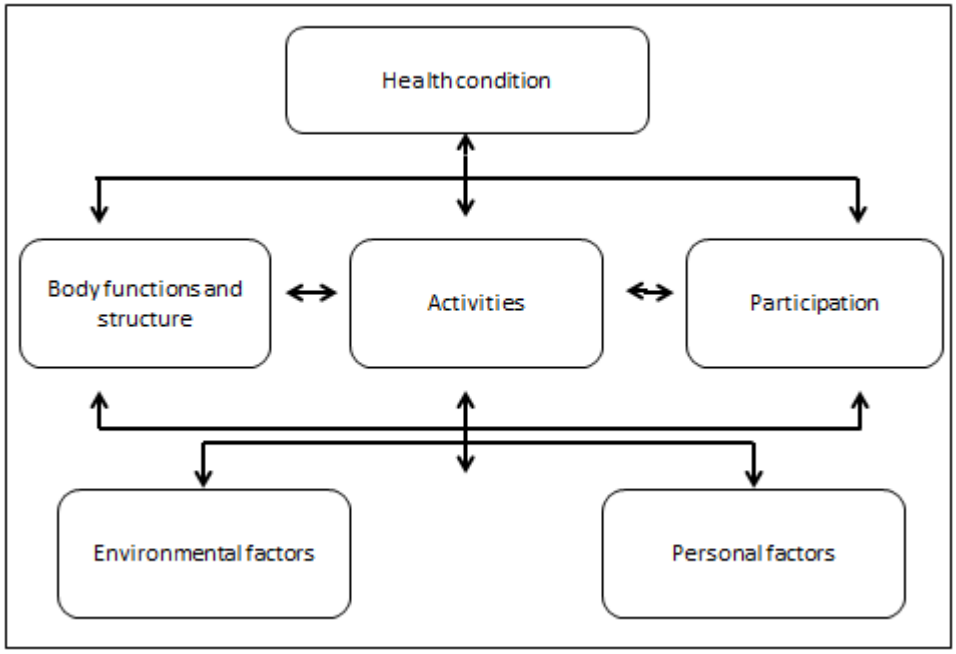
1.4.2. Conceptual framework of International Classification of Functioning

The International Classification of Functioning (World Health Organization 2001) Disability and Health model has, since its publication in 2001, become a guiding model for disability research and a key tool for understanding health-related disability (Badley 2008; Bruyere et al. 2005). Moving from a strictly medical understanding of health-related disability, the WHO has emphasized the dynamic mechanisms of such disabilities, emphasizing the interplay among biological, psychological, social, individual and environmental factors (Masala & Petretto 2008). The current ICF provides a conceptual framework comprising six different components (figure 2):

1. The 'Health condition (disorder or disease)' component refers to the medical diagnoses, disorders or health problem.
2. The 'Body functions and structure' component describes how the disease affects the structures, mechanisms, organs or parts of the body.
3. The 'Activities' component applies to the functioning of the person as a whole, e.g., being able to perform basic activities in daily life. Activities involve physical and psychological functioning, e.g.,walking, thinking, or talking.
4. The 'Participation' component refers to societal involvement which is defined by a social role (Biddle 1986) such as employment, work, leisure, parenting and community, social and civic life.
5. The 'Environmental factors' component enables the consideration of contextual factors, e.g., social benefit systems, legislation, and the work environment at the societal, group or individual level.
6. The 'Personal factors' component is attributed to the individual, e.g., social support and coping style.

The double arrows within the model illustrate that disability is a multi-factorial phenomenon that does not always have a clear cause-effect relationship. Thus, the importance of considering the dynamic relationship of all the model's components when understanding the development of health-related disability is emphasized. The ICF understands disability as an umbrella term for health-related limitations in body structures and functioning, activities, or participation in societal roles (WHO, 2001, p 12) (World Health Organization 2001).

Figure 2. Conceptual model: International Classification of Functioning (ICF)

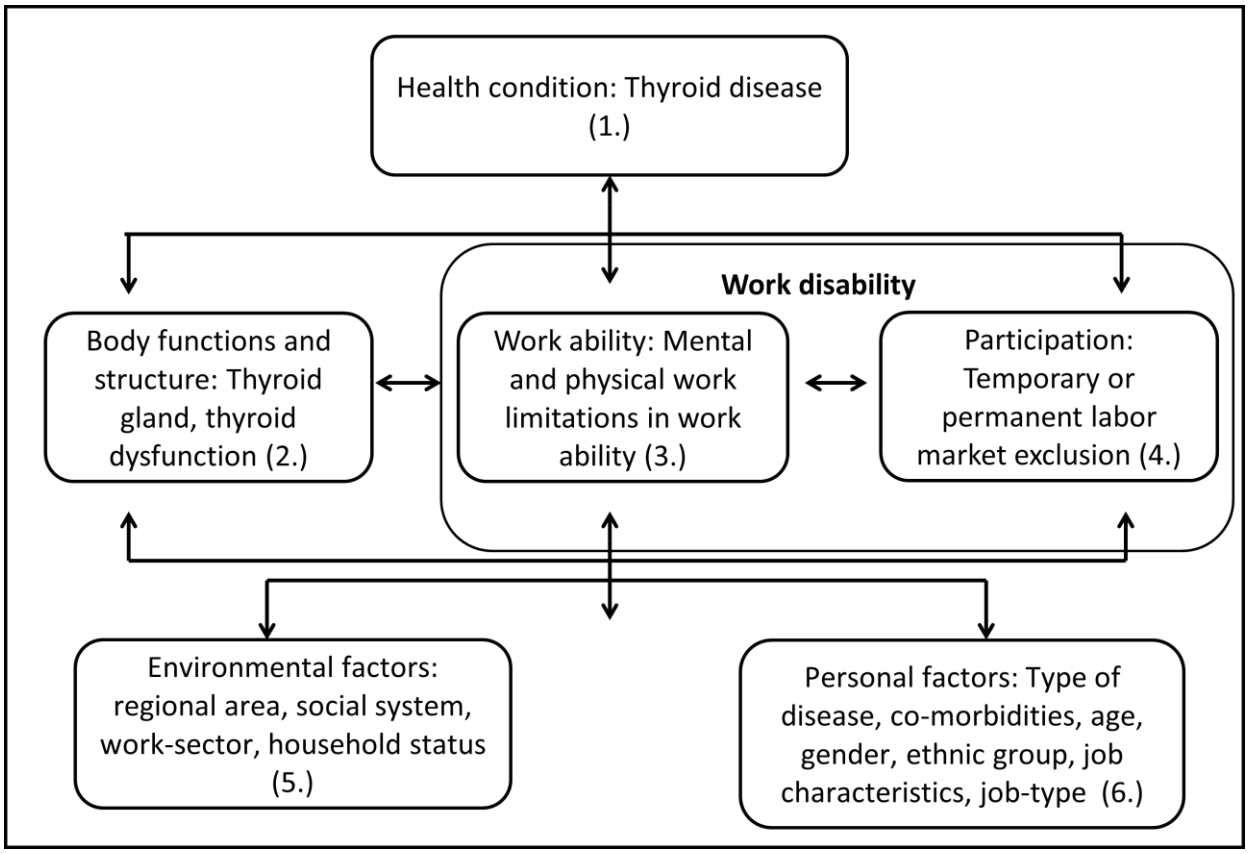


1.4.3. Adapting the conceptual framework of ICF to thyroid diseases

The conceptual framework of the ICF will be used as a theoretical model underpinning the understanding of the development of work disability in thyroid diseases. The term 'work disability' refers to the two distinct components of the ICF model: the limitations in the ability to carry out work tasks (activities) at work, similar to the term 'work functioning' or 'work ability' and limitations to the employment role (participation). Work functioning or ability can be distinguished from 'participation' because the latter describes employment as a role and not the ability to carry out a work task. Throughout this thesis, the terms 'work function' or 'work ability' will refer to experienced limitations or impaired work ability in the context of the work place. It refers to outcomes related to either generic measurements of work ability (e.g., global measures of work ability, limitations, productivity or performance) or specific measures of work limitations (e.g., limitations in the ability to carry out specific work tasks). The term 'presenteeism' will be used to describe the act or behavior that can result from having an impaired work ability: attending work while ill (Johns 2010). By contrast, the term 'absenteeism' refers to unavoidable or involuntary absence from work, such as sickness absence (Sagie 1998)

The term ‘labor market exclusion’ will refer to the participation component of the ICF and to work disability as manifest by sickness absence, unemployment and disability pension. Based on the extant literature, the factors associated with thyroid associated disability can be mapped within the ICF model (Figure 3). Thyroid diseases disrupt the thyroid gland, which affects important organs of the body, including the brain (pathway 1 to 2). Thyroid diseases affect mental and physical functions, being most pronounced in the acute phase of the disease (pathway 1 to 2 to 3), but can also persist when thyroid hormones are within the normal laboratory range and thus have no clear biomarkers (pathway 1 to 3). The few studies that have examined work disability in thyroid diseases suggest that these diseases have an impact on work ability and participation. However, the mechanisms responsible for work disability remain unclear. The impact of thyroid diseases on mental and physical functioning may affect the ability to perform activities at work (pathway 1 to 2 to 3 or pathway 1 to 3) and may affect the individual’s possibility of participating in social roles, including employment (pathway 1 -> 2 -> 3 -> 4, pathway 1->3->4 or pathway 1->4). It is possible that the mechanisms can occur in the opposite direction. For example, it is possible that external stressors such as demands to increase work pace or increasing the amount of work tasks can impact the thyroid disease negatively (e.g., pathway 5->2->1->3->4). However, because work disability in thyroid diseases is not well documented, the main focus of this thesis is examining the pathways from thyroid diseases to work disability.

Figure 3. Work disability in thyroid diseases (WHO's ICF model)



Aims of the thesis

The overall aim of this thesis was to examine whether thyroid disease causes work disability. This question was evaluated through analyses of work role function / work ability and analyses of participation / exclusion from the labor market.

The first part of the project focused on participation / exclusion from the labor market. This part of the project aimed to answer the following research questions:

Do patients with thyroid diseases have an increased risk of sickness absence, unemployment and disability pensioning?

Do the type and duration of the diseases influence sickness absence, unemployment and disability pensioning?

The second part of the project focused on work role function / work ability. This second part of the project aimed to:

Explore the illness experience of thyroid disease patients and explore what factors might play a role in work disability.

Develop and evaluate a self-rating questionnaire about work ability for patients with thyroid diseases.

Evaluate whether self-rated work ability is impaired among patients with thyroid disease.

2. Methods

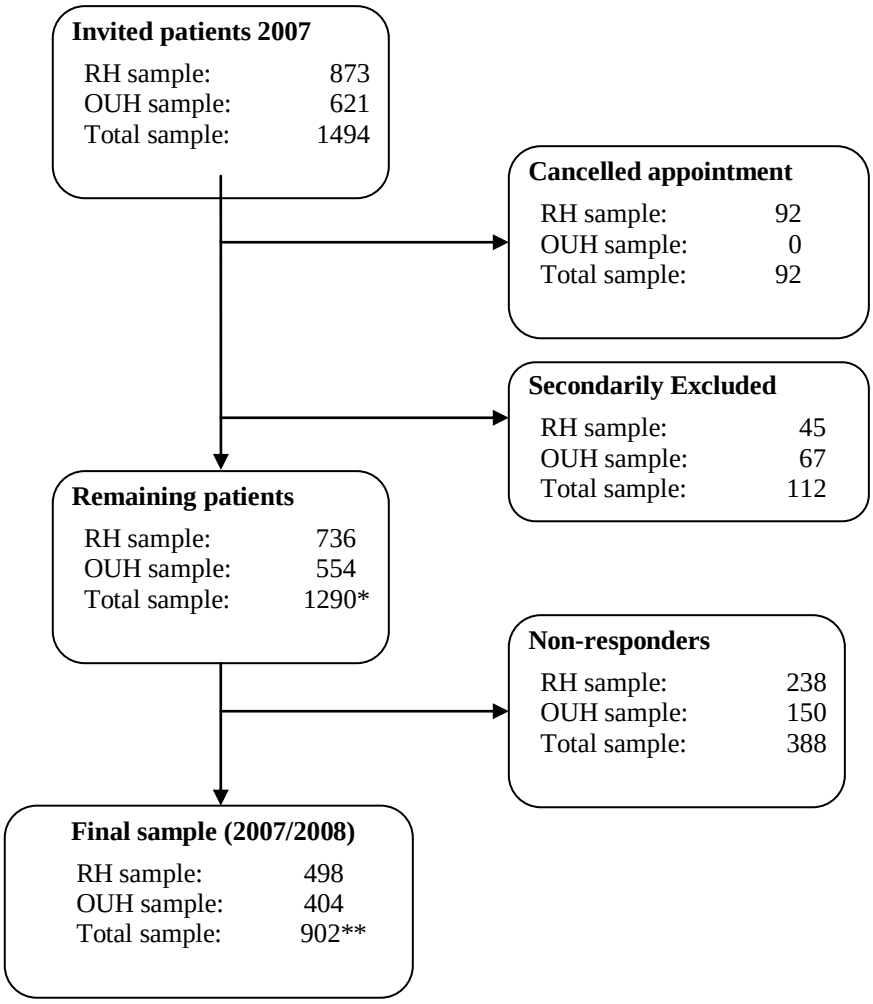
Work disability among people with thyroid diseases is examined in three studies. Because the methods of each study are also described in the three research papers (appendix 1), the aim of the methods section is to provide an overall summary of the three studies.

2.1. Summary of the designs of the three studies

2.1.1. Study 1: A register-based cohort study

Study 1 was a longitudinal register study, in which a population of treated outpatients with thyroid diseases (n=862) and their matched controls (n=7,641) from a general population sample was observed in Danish national registers of social benefits, health, and work characteristics covering the period 1994 to 2011. Figure 4 provides a flow chart of the clinical population that was recruited from Odense University Hospital and Copenhagen University Hospital (Rigshospitalet) in relation with a previous survey (Watt 2007; Watt et al. 2009). Records were traced back to 1 January 1994 to establish the earliest time of diagnosis. The data were analyzed using a multistate Cox regression model. Participants were censored at the end of the observation period on 1 April 2011, or before if they died or emigrated. Disability pensioning was regarded as an absorbing event. The patients with thyroid disease entered the analyses at the time of diagnosis. For each patient, 10 controls were selected with matching for age, gender, and region of habitation. The controls entered the analyses at the same time as the thyroid patients. The risks of sickness absence, unemployment, or disability pension and the probabilities of return to work from sickness absence or unemployment were compared with those of the controls. The underlying time variable was age. Separate risks were estimated for the first year after diagnosis and for subsequent years. Analyses were performed for the group of all thyroid patients. In addition, subgroup analyses were performed, comparing each thyroid disease subgroup with the general population. The analyses were adjusted for gender, job type, household status, immigrant status, season and time period, region of living, and co-morbidity (Paper 1, appendix 1).

Figure 4. Patient flow in the study comprising Rigshospitalet (RH) and Odense University Hospital (OUH). Recruitment procedure described in Watt 2007/Watt et al. 2009.



*Population initially included for register-based cohort study (study 1)
**Population initially included as subsample 1 for the thyPROw survey (study 3)

2.1.2. Study 2: A qualitative interview study

Study 2 was a qualitative study of 16 individual in-depth interviews with medically treated participants. Participants were purposefully selected according to their diagnosis (autoimmune hypothyroidism (n=5), Graves' hyperthyroidism without orbitopathy (n=7) and Graves' disease with orbitopathy (n=4)), length of treatment (more than six months) and age (18-65 years). The participants were asked open-ended questions about their health, thyroid disease, daily life, and work experiences.

The transcribed interviews were analyzed and major themes identified by Interpretative Phenomenological Analysis (Smith et al. 2009a; Smith 2011a). The data analysis followed four phases: 1) An initial phase of coding the transcript. This included the identification of immediate impressions, ideas or feelings emerging from each individual transcript. Here, the phenomenological principle of IPA was followed, in which the researcher gives full attention to the experiences of the participants. Codes are generated from the data rather than coding based on confirming or disconfirming pre-existing theory. A subsequent process of molding the meaning into themes was a way of accounting for the hermeneutical stance of IPA, in which the researcher 'makes sense of the participant's sense making of their own experiences'. 2) A phase of developing a structure of recurrent or interrelated themes of each individual case. 3) A phase in which the essences of the themes were generalized across participants. The guidelines suggested for this final stage by Smith (Smith 2011a; Smith 2011b) were followed. 4) A final phase in which the main themes were further developed into superordinate themes by relating them to the themes shared among the participants either within each diagnostic category or across the diagnostic categories. (Paper 2, appendix 1)

2.1.3. Study 3: ThyPROw survey

Study 3 was a cross-sectional survey (2012/2013) that included two subsamples: 1) Persons who had participated in a previous survey on quality of life with thyroid disease (Figure 4, the ThyPRO 2007/2008 survey (Watt, 2007; Watt et al. 2009)), and 2) Newly recruited persons with thyroid disease. Thus, subsample 1 allowed a follow-up of persons who had responded to a work ability item from the thyPRO 2007/2008 survey. In the 2012/2013 thyPROw survey, a work ability scale of people with thyroid diseases was developed and evaluated. Relevant items were identified through literature reviews, patient interviews (study 2), and analysis of existing data concerning thyroid-related quality of life. The questionnaire was evaluated by a panel of experts within the fields of social science and endocrinology and tested through cognitive interviews with 40 patients at Odense University Hospital and Rigshospitalet. Cognitive

interviews are a method for enhancing the reliability and validity of a questionnaire (Wilson 2005). Problems with the comprehension of different items in four domains (illness perception, management of symptoms, work limitations and management of difficulties at work) were identified in the first phase of testing. The items were revised and re-tested in phase 2, and the total questionnaire was tested and revised in phase 3 of the interviews. The questionnaire is given in Appendix 2.

The construct validity of 24 work ability items was evaluated in confirmatory factor analysis (CFA) and tests of differential item functioning (DIF). The CFA analyses fitted 3 models: 1) A base case model where all items loaded on one factor. 2) A bifactor model (Reise et al. 2007), where all items loaded on a global factor and on sub-factors defined by item content (attribution to physical role function, emotional role function, thyroid disease, general work limitations and performance). The bifactor model was revised until a satisfactory fit was achieved, and 3) A multifactor model specifying the sub-factors identified above as correlated factors and dropping the global factor. DIF tests were used to determine whether certain groups respond differently to a particular item of a test or questionnaire. DIF was tested in relation to age, gender, and thyroid disease using ordinal logistic regression tests (Zumbo 1999).

The work ability among 507 employed thyroid patients was compared with a general population sample (n=15,050) with logistic regression analyses. The work ability in thyroid diagnostic subgroups was compared through five work ability scales analyzed using linear regression. A longitudinal analysis was performed to examine whether self-reported thyroid-specific work ability predicted early retirement over four years (Paper 3, appendix 1).

An overview of the design, populations, measurements, outcomes and analyses of the three studies is provided in table 1.

Table 1. Overview of design, populations, outcomes data sources, and analysis applied in the three different studies

Studies	Design	Populations	Outcomes and data sources	Analysis
Study 1 Register-based cohort study	Longitudinal register-based cohort study (follow-up period 1994-2011)	*Thyroid population* (n=862): Patients from OUH and RH (Hypo, Hyper, GO, NTG, TNG, OT), aged 18 to 59 years *Control sample*: Random sample from general population matched to the thyroid sample by gender, age and region of living (n=7641)	Transitions between the states of work, sickness absence, unemployment, disability pension Register of Social Reimbursement (DREAM):	Multi-state model Cox regression analysis Adjusted for: gender, job type, household status, number of working hours, immigrant status, season, and years
Study 2 Qualitative interview study	Cross-sectional (purposeful sampling) one-to-one interviews at one point in time	*Thyroid population* (n=16): Patients from OUH and RH, aged 18-65 years *Criteria for sampling*: Diagnosis (hypo, hyper, GO) Treatment length (>6 months)	Main themes of importance to illness experience and work and daily life (transcribed interviews)	Interpretative Phenomenological Analysis
Study 3 Survey	Cross-sectional (external comparison with general population and internal comparison cross diagnostic sub-groups and length of disease) Longitudinal (4 year follow-up period)	*Thyroid population* (n=776/responders, n=632): Patients from OUH and RH (Hypo, Hyper, GO, NTG, TNG, OT), aged 18-59 years *Subsample 1:*ThyPRO survey 2007/2008 (T0), follow up 2012/2013 (T1) (n=460/responders, n=391) *Subsample 2:* Newly diagnosed patients 2012/201 (n=316/responders, n=241) *Population included for comparative analyses:* employed responders (n=507) *Population included for longitudinal analysis:* a. responders of work ability item T0 (n=379) b. Responders of work ability item at T0 and T1 (n=269) *Control population* (n=15050): Employed responders from the general population, aged 18-59 years from the National Work and Health Survey, 2012	Work ability scales: Role physical and role emotional (SF-36) Thyroid specific work limitations (ThyPRO and newly developed items) Work limitations (developed items) Performance (DANES, 2008 DWECS,2010) Three single global work ability items (Work Ability Index)	Confirmatory Factor Analysis Differential Item Functioning Logistic regression Linear regression Adjusted for: age, gender, job-type, job-sector

Abbreviations: DANES, 2008: Danish National working Environment Survey, DREAM: Danish Register for Evaluation of Marginalization, DWECS, 2010: The Danish Work Environment Cohort Study, OUH: Odense University Hospital, RH: Rigshospitalet, ThyPRO: Patient Reported Outcomes questionnaire for patients with thyroid diseases. Hypo: Autoimmune hypothyroidism, Hyper: Graves' hyperthyroidism, GO: Graves' orbitopathy, NTG: Non-toxic goiter, TNG: Toxic nodular goiter, OT: Other thyroid disaeses

2.2. Background and considerations of the applied methods

This thesis comprised one qualitative and two quantitative studies. The terms 'mixed methods'(Klassen et al. 2012) or 'multi-methods' (Tashakkori & Teddlie 2010) are used to describe the application of both quantitative and qualitative methods or, in some cases, the application of multiple quantitative or qualitative methods. The development of the work ability scale in study 3 was built on the factors of importance to disability found in study 2. This combination of methods can be described as sequential (Klassen et al. 2012; Malterud 2001a). One major advantage of applying mixed methods is the possibility of strengthening the validation of the results via triangulation (Creswell 2010; Malterud 2001b). Triangulation is a procedure of validation where researchers search for a convergence of results from multiple and different methodologies or sources of information (Creswell 2010; Malterud 2001b). Triangulation can be used to evaluate agreement within methods (e.g., multiple scales in a survey) or across multiple methods (e.g., across two or more different research methods) (Todd et al. 2004). The results of the three different studies are combined (triangulated) in this thesis by within method- (studies 1 and 3) and cross method validation (studies 1, 2 and 3).

2.2.1. Study 1

In study 1, an epidemiological research methodology was applied to observe the risk of exclusion from the labor market for people with thyroid diseases. Exclusion from the labor market was assessed through social transfer payments for long-term sick leave, unemployment or disability pensioning registered in the Danish Register for the Evaluation of Marginalization (DREAM). In doing so, work disability was defined by the laws of the Danish social security system. DREAM has been evaluated to be suitable for the follow-up of social consequences of disease (Hjollund N.H. et al. 2007). Although this study allowed the evaluation of labor market exclusion, the study does not evaluate whether the work ability is impaired and may result in decreased productivity while at work. Also, it does not cover the factors of importance that help people manage work disability and avoid labor market exclusion.

The risk of transition between five work-related states was estimated using a multi-state proportional hazards model (Pedersen et al. 2012). This model allows for the investigation of transitions between several states and multiple events per subject. Multi-state models estimate the probabilities of transitioning from one state (e.g., work) to another (e.g., sickness absence) (Andersen 2002b) and are increasingly used because they allow investigation of the dynamic

and complex interplay among factors involved in health and labor market outcomes during the course of a disease. A multi-state model has been developed to examine labor market outcomes (Pedersen et al. 2012).

2.2.2. Study 2

The qualitative research methodology applied in study 2 builds on the theoretical frame of Interpretative Phenomenological Analysis (IPA). IPA is a qualitative method rooted in hermeneutics and phenomenology (Smith et al. 2009b). In recent years, IPA has been widely applied within health psychology (Smith 2011a) to explore illness experiences in a wide range of medical conditions in different contexts (Reid et al. 2005). Qualitative methods give access to the idiosyncratic subjective experience of the phenomena under study along with the possibility of an in-depth understanding of the complex mechanisms involved in the development of disability in thyroid diseases. Qualitative methods can provide different but complementary perspectives within the field of medicine (Barbour 2000), and no published study has previously explored the lived experience of thyroid diseases. The qualitative interview study was conducted to gain a more comprehensive understanding of the complex relation between symptoms of thyroid diseases, individual and contextual psychosocial factors, and functioning in work and daily life. Although the major advantage of qualitative methods is the possibility to gain insight into processes and mechanisms, the disadvantage is often limited generalizability beyond the individual level, and quantitative methods are often needed to test the theories or hypotheses generated from such studies.

The qualitative study had a cross-sectional design with purposeful sampling of diagnosis, treatment length and age. The applied sampling strategy was in line with a criterion-based approach (Kuzel 1999), in which the criteria for selection are defined before the data are gathered. Three diagnostic subgroups were chosen, namely, autoimmune hypothyroidism and hyperthyroidism (with and without orbitopathy), as these were expected to be the most severe diseases. Moreover, hypo- and hyperthyroidism were expected to be two different clinical conditions that could be expected to manifest themselves differently at work and in daily life. By selecting participants who had passed the acute phase of the disease (minimum treatment length = 6 months) within the working age (18-65 years), the lived experience of work and daily life among people who had passed the acute phase of thyroid diseases could be assessed. There are no general rules of the sample size in qualitative methods, but in some studies applying

homogenous samples, five to eight participants will often be adequate (Kuzel 1999). With an idiographic approach, IPA aims to provide rich and detailed data and, therefore, most often draws on small groups of people or even single case studies (Smith et al. 2009b). In this study, therefore, samples with at least four participants in each diagnostic sub-group were recruited.

2.2.3. Study 3

Study 3 builds on a health-related quality of life research methodology. Rooted in a social scientific paradigm this methodology provides a framework in which the subjective experience of symptoms, functioning and well-being can be quantified and summarized at group level, allowing for comparison across groups. Self-reported measurements of work ability provide access to the limitations experienced at the workplace and self-reported measurements can be good predictors of health- and work-related outcomes (Bjorner et al. 2005; Sell 2009). Thus the three different research methodologies of the studies can provide different but complementary perspectives on whether thyroid disease causes work disability.

2.3. Theoretical assumptions behind the three studies

The theoretical assumptions of the three studies are described within the conceptual framework of ICF (figure 1). Study 1 examines whether thyroid disease cause labor market exclusion (pathway 1 to 4, figure 1) by either sickness absence, unemployment or disability pension or by difficulties with returning to work from sickness absence or unemployment (participation). Study 3 examines whether the work ability among people with thyroid diseases is decreased (pathway 1 to 3, figure 1). Also, the longitudinal analysis of study 3 allows the examination of the sequential theoretical assumption that thyroid associated limitations in work ability increase the risk of labor market exclusion or difficulties returning to work (pathway 1 to 3 to 4, figure 1). Personal and environmental factors might affect both the work ability (pathway 5/6 to 3 and pathway 5/6 to 1) and the risk of labor market exclusion (pathway 5/6 to 4 and pathway 5/6 to 4) and can therefore be viewed as confounders. Because the qualitative research methodology of study 2 was inductive and not driven by pre-existing theories or hypotheses, this model only applies to the theoretical assumptions of studies 1 and 3.

3. Summary of the results

This section will provide a brief summary of the results of the three studies.

3.1 Study 1: A register-based cohort study

Table 2 shows the adjusted HRs of transitions from work, sickness absence, unemployment and early retirement for patients with thyroid disease compared with the control population within the first year and in subsequent years.

3.1.1. Sickness absence

When analyzing the combined group, thyroid patients had a significantly increased risk of sickness absence within the first year of diagnosis compared with the general population. In subgroup analyses, toxic nodular goiter, Graves' hyperthyroidism, and Graves' orbitopathy had significantly increased HRs of sickness absence.

In subsequent years, the probability of sickness absence across thyroid diseases decreased but remained significantly higher than the general population. In subgroup analyses, the probability of sickness absence was only significantly higher in patients with Graves' orbitopathy.

3.1.2. Return to work from sickness absence

Within the first year of diagnosis, the analyses of all thyroid diseases showed that patients had a significantly decreased probability of returning to work from sickness absence compared with the general population. Separate analyses of diagnostic sub-groups showed that patients with toxic nodular goiter and autoimmune hypothyroidism had a significantly lower probability of returning to work from sickness absence.

In the analyses of subsequent years, the probability of returning to work from sickness absence improved for the combined group compared with the first year, but remained significantly lower than that of the general population. In sub-group analyses, the probability of return to work from unemployment only remained significantly lower than the general population for patients diagnosed with Graves orbitopathy.

Table 2. Probability of the five work transitions for patients with different thyroid diagnoses compared to the control population

		Sickness Absence (SA)		Return to work from SA		Unemployment (U)		Return to work from U		Disability pension	
		HR	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
Entire thyroid population	< 1 Year	**1.86**	**(1.47-2.36)**	**0.77**	**(0.60-0.99)**	1.18	(0.86-1.61)	0.88	(0.65-1.17)	**2.76**	**(1.47-5.18)**
	> 1 Year	**1.18**	**(1.03-1.35)**	**0.81**	**(0.69-0.94)**	**1.34**	**(1.09-1.66)**	1.06	(0.86-1.31)	1.17	(0.87-1.58)
Separate analysis according to diagnostic sub-group											
Non-toxic goiter	< 1 Year	1.24	(0.81-1.90)	1.40	(0.90-2.17)	1.33	(0.78-2.26)	1.06	(0.60-1.87)	*	
	> 1 Year	0.92	(0.76-1.11)	1.11	(0.85-1.44)	**1.48**	**(1.11-1.99)**	1.31	(0.99-1.74)	0.68	(0.41-1.13)
Toxic nodular goiter	< 1 Year	**1.97**	**(1.12-3.45)**	**0.57**	**(0.33-0.98)**	0.65	(0.25-1.68)	0.79	(0.33-1.87)	*	
	> 1 Year	0.82	(0.60-1.13)	0.66	(0.42-1.04)	1.41	(0.88-2.27)	1.10	(0.68-1.79)	0.95	(0.41-2.21)
Graves' hyperthyroidism	< 1 Year	**1.92**	**(1.10-3.34)**	0.67	(0.41-1.11)	1.28	(0.71-2.30)	0.77	(0.48-1.23)	*	
	> 1 Year	1.31	(0.99-1.74)	0.75	(0.52-1.08)	1.49	(0.75-2.96)	1.14	(0.55-2.34)	1.20	(0.58-2.49)
Graves' orbitopathy	< 1 Year	**6.96**	**(4.22-11.5)**	0.58	(0.31-1.10)	0.51	(0.14-1.85)	0.39	(0.13-1.15)	*	
	> 1 Year	**2.05**	**(1.46-2.88)**	**0.52**	**(0.40-0.67)**	0.90	(0.49-1.68)	**0.51**	**(0.35-0.73)**	**4.40**	**(2.65-7.29)**
Autoimmune hypothyroidism	< 1 Year	1.36	(0.81-2.26)	**0.56**	**(0.36-0.86)**	1.12	(0.58-2.17)	0.95	(0.52-1.73)	*	
	> 1 Year	1.24	(0.90-1.71)	0.79	(0.56-1.12)	1.16	(0.79-1.73)	0.90	(0.68-1.19)	1.46	(0.80-2.69)
Other thyroid disease	< 1 Year	1.63	(0.78-3.42)	1.48	(0.53-4.16)	1.75	(0.81-3.75)	0.80	(0.45-1.42)	*	
	> 1 Year	1.68	(0.98-2.88)	1.13	(0.67-1.89)	1.09	(0.60-1.98)	0.88	(0.51-1.51)	0.49	(0.12-1.96)

* Data insufficient for estimation/ Too few instances to allow for estimation
Statistically significant estimates shown in **bold**.

3.1.3. Unemployment

The overall analyses did not show any significantly increased risk of unemployment in the first year of diagnosis. In subsequent years, the risk of being unemployed was significantly higher in analyses of all thyroid diseases. In the sub-group analyses, patients with non-toxic goiter had increased risk of unemployment one year after diagnosis.

3.1.4. Return to work from unemployment

For the combined group, no significant higher or lower probabilities of return to work, once unemployed, were observed in the first year of diagnosis or in subsequent years. However, in the subgroup-analyses, patients with Graves' orbitopathy had a lower probability of returning to work from unemployment after more than a year with the disease.

3.1.5. Disability pension

The risk of disability pension was significantly increased in the first year of diagnosis in the overall analysis, but no significant higher risks were observed in subsequent years. There were insufficient data to analyze the risk of disability pension in sub-group analysis within the first year of diagnosis. After a year with the disease, the risk of disability pension was significantly higher in persons with Graves' Orbitopathy.

3.2. Study 2: A qualitative interview study

Three superordinate themes emerged from the analysis: 1. Losing control over physical and mental states, 2. Ambiguous signs of disease, and 3. Negotiating sickness.

3.2.1. Losing control over physical and mental states

The first superordinate theme concerned the illness experiences of the different medical conditions. A defining feature of experiencing hypothyroidism was feeling drained. An essential part of having hyperthyroidism was the feeling that the body never rested and a feeling of being emotionally out of control. The cosmetic changes sometimes experienced by patients with Graves' orbitopathy could implicate a feeling of being self-conscious, leading to the avoidance of social situations. The illness experiences entailed a loss of control over mental and physical

states, implicating a loss of identity and the coherence and meaning normally gained by being able to regulate emotions, sleep or physical appearance.

3.2.2. Ambiguous signs of disease

The second superordinate theme concerned the ambiguity experienced when participants attempted to make sense of their symptoms as medical signs of disease. The participants experienced the medical conditions hypo- and hyperthyroidism (but not the cosmetic changes) as diffuse, hidden and essentially merging with everyday events. This left the participants in a grey area in which they did not feel sick in a medical sense but did not feel well either. Rather, they were left between illness and disease.

3.2.3. Negotiating sickness

The third superordinate theme concerned the process by which the majority of participants negotiated their status of being sick. The diffuse nature of the medical conditions of feeling hypo- and hyperthyroid conditions (not cosmetic changes) created a need to clarify the illness experience via biomedical evidence. However, the signs of illness are not usually founded on biomedical evidence resulting in an uncertain sickness status. An uncertain sickness status had emotional consequences and made the participants disclaim the need for sickness absence, to take off early or to reorganize work tasks. By contrast, the legitimization of illness experiences made it easier to justify absence from work and work limitations while at work.

3.3. The ThyPROw survey

3.3.1. Confirmatory Factor Analysis and analysis of differential item function

Table 3 summarizes the results from the Confirmatory Factor Analysis (CFA). In a one factor model, all items loaded strongly on the common factor, but the model did not achieve good fit. A bi-factor model with one global and five local factors achieved good fit, but the loadings on one of the local factors where stronger than the loadings on the global factor, which suggested multidimensionality. A multifactor model with five correlated factors was identified as the best model (table 3). This scale structure was pursued with one exception. Only items from the SF-36 scale were included in the role physical (RP) scale because the RP items, in contrast to the global work ability items, ask about limitations in relation to “work or other daily activities”. These items are also relevant to persons not currently working. The results from the Differential Item Function (DIF) analysis led to removal of two items from the Work Limitations (WL) scale.

Table 3. Factor analysis of work ability items in the thyroid patient cohort

Items		One factor	Bi-factor models						Multi-factor models				
			Global	RP	RE	THY	WL	PERF	RP	RE	THY	WL	PERF
SF36_RP1	Cut down ... amount of time …	0.91	0.87	0.35					0.94				
SF36_RP2	Accomplished less …	0.88	0.87	0.30					0.92				
SF36_RP3	... limited in the kind of work …	0.92	0.82	0.52					0.94				
SF36_RP4	... difficulty performing the work …	0.96	0.88	0.43					0.98				
G_PHYS	Work ability vs. phys demands …	0.68	0.64	0.32					0.70				
G_WAI	Current work ability score (0-10)	0.78	0.84						0.85				
SF36_RE1	Cut down ... amount of time …	0.90	0.78		0.58					0.96			
SF36_RE2	Accomplished less …	0.81	0.72		0.57					0.91			
SF36_RE3	Did work … less carefully than usual	0.88	0.80		0.51					0.97			
G_PSY	Work ability vs. mental demands …	0.72	0.69		0.11			0.21	0.27	0.34			0.28
THY_DIF	Difficulties in doing your job …	0.83	0.88			0.22			0.39		0.59		
THY_PLAN	Planned your work differently	0.82	0.79			0.52					0.95		
THY_OFF	Taken off early	0.77	0.74			0.55					0.90		
THY_INVOLVE	Involved ... supervisor / colleagues	0.74	0.73			0.46					0.87		
WL_HOURS	… necessary number of hours	0.86	0.86				0.31					0.96	
WL_BREAK	Work without ... extra breaks	0.83	0.80				0.42					0.91	
WL_ROUTINE	Stick to a routine or plan	0.82	0.74				0.59					0.91	
WL_TEMPER	Control your temper	0.52	0.50				0.45					0.62	
WL_CONC	Concentrate on the work	0.76	0.69				0.54					0.85	
P_LOAD	Handle a high work load	0.71	0.59					0.60	0.27				0.68
P_WELL	Do your work well	0.69	0.36					0.77					0.81
P_ERROR	Work without making mistakes	0.66	0.39					0.68					0.79
P_DECIDE	Make quick decisions	0.64	0.43					0.73					0.86
P_CONC	Concentrate on the work	0.70	0.59					0.60		0.27			0.73
Local correlations			G_PSY with G_PHYS: 0.28, G_PSY with G_WAI 0.12, P_WELL with P_ERROR: 0.15						G_PSY with G_PHYS: 0.27, G_PSY with G_WAI 0.15, P_WELL with P_ERROR: 0.18				
Factor Correlations													
RE									0.75				
THY									0.72	0.68			
WL									0.77	0.73	0.78		
PERF									0.47	0.32	0.44	0.39	
Model fit													
CFI		0.792	0.983						0.974				
RMSEA		0.263	0.070						0.076				

RP: Role Physical, RE: Role Emotional, THYR: Thyroid specific limitations, WL: Work Limitations, PERF: Performance, CFI: Conparative Fit Index, RMSEA: Root-Mean-Square Error of Approximation

3.3.2. Comparisons with the general population

Table 4 shows the adjusted Odds Ratios (ORs) for the analyses of the 3 single items. In analyses comparing all the thyroid diseases with the general population, only the global item on work ability showed a significant difference. In the subsequent analysis by clinical subgroups, patients with Graves' disease, autoimmune hypothyroidism, and other thyroid diseases had significantly lower scores than the general population on the global work ability item. Patients with non-toxic goiter rated their work ability in relation to physical and mental demands better than the general population, while patients with Graves' hyperthyroidism rated their work ability as worse with respect to mental demands. The global item on work ability was best at discriminating between the thyroid and the general population

Table 4. Work ability (WA) compared to the general population. Odds Ratio (OR) for a 1 category LOWER score with 95 percentage Confidence Intervals (CI)

	WA Global		**WA with respect to mental demands**		**WA with respect to physical demands**	
Effect*	OR	95%CI	OR	95%CI	OR	95%CI
All thyroid diseases (n=503)	**1.58**	**(1.33-1.88)**	0.89	(0.75-1.07)	0.86	(0.72-1.02)
Chi-square (1 DF)		**26.9**		1.5		2.9
Non-toxic goiter (n=186)	1.11	(0.84-1.48)	**0.71**	**(0.53-0.95)**	**0.73**	**(0.54-0.98)**
Toxic nodular goiter (n=45)	0.93	(0.52-1.66)	0.90	(0.50-1.63)	0.84	(0.47-1.53)
Graves' disease (n=99)	**3.14**	**(2.16-4.57)**	**1.79**	**(1.22-2.63)**	1.44	(0.98-2.12)
Graves' orbitopathy (n=32)	1.79	(0.92-3.51)	0.67	(0.34-1.35)	0.66	(0.32-1.35)
Autoimmune hypothyroidism (n=115)	**1.68**	**(1.18-2.4)**	0.83	(0.58-1.19)	0.71	(0.49-1.03)
Other thyroid disease (n=26)	**2.12**	**(1.06-4.26)**	0.66	(0.32-1.36)	1.24	(0.60-2.56)
Chi-square (6 DF)		**50.8**		**18.8**		**13.2**

Analyses controlled for: age, gender, job type, and work sector.
Significant differences compared to the sample of the general population in bold.
* Reference group: general population (n=15408), female, age 45, job with low cognitive demands in the knowledge and health sector

3.3.3. Internal analysis

Table 5 shows the results of the scale level analyses comparing the non-toxic goiter group with the other clinical subgroups and patients diagnosed less than a year with patients being diagnosed for more than a year. The RP and RE scales are scored to achieve a mean of 50 and a standard deviation of 10 in the US general population. In Danish general populations, the average scores are about 54. The THYR, WL, and PERF scales are scored on the scale from 0 to 100 (100= best work ability).

Patients with Graves' disease reported significantly lower work ability than people with non-toxic goiter on the SF-36 RP and role emotional (RE), limitations with attribution to thyroid disease (THY), and work limitations (WL) scales. Patients with autoimmune hypothyroidism reported significantly lower work ability than people with non-toxic goiter on the RE and THY. No significant results were observed for patients from the other diagnostic groups (toxic goiter, Graves' orbitopathy, 'other thyroid diseases'). The work ability was reported to be significantly lower among people diagnosed for less than a year on the RP, RE, THY and performance (PERF) scales but not the WL scale. The THY scale had most statistical power.

3.3.4. Longitudinal analysis

Adjusting for age, gender and education, participants who assessed their work ability as impacted at T0 were five times more likely to be excluded from the labor market at T1 [OR=5.0, 95% CI: 2.7-9.1] compared with participants who had no work limitations at T0. Among the 269 participants who answered the thyroid-specific work ability item both at T0 and T1, the association between the two scores was strong [OR=4.4, 95% CI 2.2-9.8, adjusting for age, gender, and education].

Table 5. Analysis of work ability for thyroid disease subgroups

	Role Physical (RP)		**Role Emotional (RE)**		**Thyroid specific limitations (THYR)**		**Work Limitations (WL)**		**Performance (PERF)**	
Parameter	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**	**Est**	**95%CI**
Comparison group*****	52.8	(50.8/54.8)	52.7	(50.6/54.9)	99.4	(95.7/100.0)	87.7	(82.2/93.3)	56.8	(52.8/60.8)
Toxic nodular goiter (n=45)	-1.8	(-4.8/1.2)	-1.8	(-5.1/1.4)	-5.1	(-10.8/0.5)	-2.7	(-11.1/5.7)	-1.2	(-7.2/4.9)
Graves' disease(n=99)	**-4.0**	**(-6.3/-1.7)**	**-2.8**	**(-5.2/-0.4)**	**-11.4**	**(-15.6/-7.2)**	**-9.4**	**(-15.7/-3.0)**	-4.2	(-8.7/0.4)
Graves' orbitopathy (n=32)	-1.2	(-4.7/2.2)	-3.5	(-7.2/0.1)	-5.2	(-11.6/1.2)	-2.7	(-12.5/7.0)	3.6	(-3.4/10.6)
Autoimmune hypothyroidism (n=115)	-2.1	(-4.2/0.1)	**-3.4**	**(-5.7/-1.2)**	**-4.2**	**(-8.2/-0.2)**	-4.5	(-10.5/1.5)	-1.0	(-5.3/3.3)
Other thyroid diseases (n=26)	-1.9	(-5.4/1.7)	-1.2	(-4.9/2.6)	-1.4	(-7.9/5.2)	-5.8	(-15.6/4)	-3.5	(-10.5/3.6)
F-value (5 DF)	**2.5**		**2.3**		**5.9**		1.7		1.2	
Disease < 1 year	**-2.6**	**(-4.4/-0.8)**	**-2.2**	**(-4.1/-0.3)**	**-5.9**	**(-9.3/-2.6)**	-4.2	(-9.2/0.8)	**-3.8**	**(-7.4/-0.2)**
F-value (1 DF)	**8.3**		**5.4**		**12.1**		2.7		**4.2**	

Analyses controlled for: age, gender, job type, and work sector.

* Patients with non-toxic goiter (n=223) through more than 1 year, female, age 45, job with low cognitive demands in the knowledge and health sector

Significant differences compared to other thyroid disease subgroups in bold.

4. Discussion

Key methodological and theoretical issues related to each of the three studies are discussed in the three papers (appendix 1). Therefore this discussion will focus on the key issues relevant for the main findings.

Within method triangulation is a method that examines the reliability of data by, e.g., cross-checking for internal consistency in multiple items measuring the same construct (Todd et al. 2004), as was the case in studies 1 and 3. Cross method triangulation searches for validation across results from multiple methods (Todd et al. 2004). Therefore I will begin by summarizing findings across studies and compare my findings with results from other researchers. Then I will discuss key methodological and theoretical issues across studies. Although cross method triangulation is a way of strengthening the validity of the findings of the three studies, it cannot account for major methodological flaws in each of the three studies. Therefore I will continue with an evaluation of the main strengths and weaknesses of each study. By so doing, future research perspectives and practical implications will be inferred. Finally, the findings of this study will be concluded.

4.1. Discussion of the main findings across all thyroid diseases

The register-based study showed that persons with thyroid diseases have a higher risk of being excluded from the labor market and a lower chance of returning to work from sickness absence compared with people from the general population. The risks were most pronounced in the first year after diagnosis but remained significant in subsequent years. Also, significantly increased risks of unemployment and disability pension were observed after a year with the diagnosis compared with the general population. Thus, the results of the register study supported the assumption that thyroid disease can cause work disability by increasing the risk of temporary and permanent labor market exclusion, as conceptualized by the ICF model.

Study two showed that the way the thyroid diseases are experienced and conceptualized plays an important role in the management of work disability. In so far as the signs of hypo- and hyper-thyroidism were experienced as hidden, diffuse and merging with everyday events, they were difficult to legitimize as true causes of work disability for the person experiencing them. Often, the signs of hypo- and hyperthyroidism were not confirmed by medical evidence, which further

augmented experiences of an uncertain sickness status. The de-legitimization of the signs of hypo- and hyperthyroidism made the work disability difficult to manage and made persons disclaim their need for sick leave or difficulties staying for the required hours. This study suggests that work disability in hypothyroidism and hyperthyroidism (but not the cosmetic changes following orbitopathy) might lead to the action of attending work while ill (presenteeism) as oppose to absenteeism (sickness absence). Also, this study suggests that questionnaire items measuring work disability with attribution to the thyroid disease or attribution to health issues would be difficult for the participants to distinguish from the impact of everyday life.

In contrast to the final suggestions made from study 2, the findings from the survey showed that items with disease attribution most effectively measured thyroid associated work ability. The analyses of study 3 evaluated different ways of assessing work ability among people with thyroid diseases. The results from Confirmatory Factor Analysis showed that the different items were best summarized in a five factor structure:

1. Role limitations with attribution to physical health (SF-36 RP scale).
2. Role limitations with attribution to emotional problems (SF-36 RE scale).
3. Work limitations with attribution to thyroid disease (THY scale).
4. Work limitations in particular areas that were identified in qualitative interviews to be a particular challenge for thyroid patients. These items did not include attribution to thyroid disease or health (WL scale).
5. Work performance without attribution to thyroid disease (PER scale).

In comparisons of disease subgroups, the THY scale (work disability attributed to the thyroid disease) provided the greatest statistical power in distinguishing the different clinical subgroups. The two other scales that used attribution to physical health (RP) and emotional wellbeing (RE) also distinguished between clinical subgroups, but with less statistical power. In contrast, the two scales without health attribution (WL and PER) did not show significant differences between the clinical groups.

In analyses comparing measurements on three generic items of work ability of all the thyroid diseases with the general population, work ability measured on a global item was significantly lower among people with thyroid disease. In contrast, two items on work ability with respect to physical and mental work demands showed a non-significant tendency for thyroid patients to rate

their work ability as better than the general population. It is possible that thyroid patients interpret the phrase “demands of your job” to include demands posed by their disease, rendering their responses to these two questions incomparable with responses from the general population. Thus, I regard the responses to the global item on work ability as the most trustworthy suggesting that thyroid disease has a negative impact on work ability.

The thyroid-specific work limitations item (ThyPRO) also provided good predictive validity: Self-rated work disability predicted work disability and labor market exclusion (early retirement and unemployment) within the next four years.

Thus, the survey results also supported the theoretical assumptions conceptualized by the ICF model that thyroid disease can impair work role function/work ability, which can subsequently cause exclusion from the labor market.

Work disability among people with a wide range of thyroid diseases has not previously been evaluated systematically in the research literature. Together the three studies supported the theoretical assumptions made in the ICF model (section 1.4.3.): Thyroid diseases can cause work disability, manifested as lowered work ability/work function and/or as subsequent exclusion from the labor market.

4.2. Discussion of the main findings for the diagnostic sub-groups

The analyses of diagnostic subgroups suffer from a general problem: the sample size was limited for some groups, in particular Graves’s orbipathy, nodular toxic goiter and other thyroid diseases, limiting the statistical power of subgroup analyses for these groups. Thus, the results of subgroup analyses can be expected to be less consistent than results for the total sample. On the other hand, clinical experience, results from the qualitative study, and results from the subgroup analyses themselves suggest that there is important subgroup differences in the association between thyroid disease, work ability, and participation in the labor marked. For this reason, results for each diagnostic subgroup are summarized below. In reviewing these results, it is important to bear in mind that lack of a significant association is not a proof of a lack of association.

4.2.1. Graves' Orbitopathy

Study 1 showed that people with Graves' orbitopathy consistently had the highest risks of labor market exclusion across different labor market outcomes (sickness absence, return to work from sickness absence and unemployment) among the diagnostic groups, both within the first year of diagnosis and in subsequent years. Graves' orbitopathy was the only diagnostic sub-group that also had increased risk of permanent labor market exclusion by disability pension. These findings correspond well with previous studies documenting that Graves' orbitopathy has a serious impact on daily functioning (Kahaly et al. 2002; Ponto & Kahaly 2012; Terwee et al. 2002) and is associated with worse work role functioning (Kahaly et al. 2005). It also predicted the worst labor market outcomes among other diagnostic thyroid sub-groups (Ponto et al. 2013). These findings also correspond well with the conceptual framework of the ICF model; the symptoms of Graves' orbitopathy can impair the work ability, which subsequently leads to difficulties retaining the link to employment. These results also correspond well with the suggestions made from the qualitative study: That the nature of the symptoms of Graves' orbitopathy was easily identified as thyroid associated disability that would lead to absenteeism.

However, the results of study 3 showed no significant impact on work ability for people with Graves' orbitopathy, compared to people from the general population or compared to people with non-toxic goiter. A possible explanation for this result is selection bias due to non-response from people who had already left the labor market, similar to the healthy worker effect (Li & Sung 1999). Also, a lack of statistical power might explain the lack of findings of study 2. The global work ability item as well as four of five scales did show an impact of Graves' orbitopathy on work ability, but because the sample was small (n=32) none of the results were significant.

4.2.2. Graves' hyperthyroidism

In study 1, the risk of labor market exclusion was only significantly worse than the general population on one outcome (sickness absence), and this risk was only observed within the first year of diagnosis. In subsequent years, the hazard rates were at the same level as- or worse than the rates for the total group and the results were non-significant. In study 3, subjects with Graves' hyperthyroidism reported the worst extent of work limitations consistently across the work ability items. These work disabilities were most pronounced within the first year of disease. In study 2,

‘the body never rests’ and ‘being emotionally out of control’ were essential parts of experiencing hyperthyroidism. These experiences were diffuse and hidden, and despite their experienced impact on daily role function subjects found it difficult to convert these signs of illness into legitimate claims of absenteeism.

One other study has shown similar work role limitations in hyperthyroidism (Bianchi 2004), and (despite methodological limitations) one other study suggested that people with hyperthyroidism were at risk of temporary and permanent labor market exclusion after treatment was initiated (Fahrenfort et al. 2000).

It is possible that the impact of Graves’ disease on the risks of labor market exclusion is limited to the first year. In so far as the impact on work disability continuous after the first year of diagnosis, subjects might be able to compensate for their symptoms and, despite the experienced impact on work ability, might be able to avoid the social consequences of labor market exclusion. As the qualitative study suggested, it is also possible that persons with Graves’s disease find it hard to justify frequent sickness absence in the long run. Lack of recognition of the diffuse and hidden symptoms was an essential experience related to Graves’ disease. Whereas the unemployed and sick-listed participants experienced stigma in relation to their disabilities, employed subjects feared the stigma of not being able to ascribe their thyroid disease as a true cause of their work limitations.

To my knowledge, no other study has explored the illness experience of people with thyroid disease. Yet parallels can be drawn to recent findings regarding the stigma experienced by people with medical conditions which also can be difficult to medically validate, such as chronic fatigue syndrome, chronic pain, or medically unexplained conditions (Aldrich et al. 2000; Kleinman & Kleinman 1991; Scambler & Hopkins 1986; Smith & Osborn 2007; Ware 1992; Werner & Malterud 2003).
Nevertheless, the most likely reason for the non-significant results for long term impact in study 1 is a lack of statistical power to predict rare outcomes such as disability pensions or unemployment.

4.2.3. Toxic nodular goiter

In study 1, the higher risk of labor market exclusion (sickness absence and/or return to work from sickness absence) among people with non-toxic goiter was only observed within the first year of diagnosis. Although a general tendency of reporting lower work ability across the scales was

observed in study 3, no significant differences were found. Again, a small sample size (n=45) makes it difficult to reliably interpret these results. Although one previous study reported the impact of hyperthyroidism on work role functioning (Bianchi, 2004), and previous studies have shown that HRQOL (Watt T et al. 2006) can be impacted, no clear distinction between Graves' disease and toxic nodular goiter has been made consistently in the literature.

4.2.4. Discussion of the main findings of autoimmune hypothyroidism

The risk of labor market exclusion (return to work from sickness absence) was limited to the first year of diagnosis among people with autoimmune hypothyroidism. The risks of labor market exclusion were elevated consistently across findings after the first year of diagnosis, but were not significant. Study 3 showed that people with autoimmune hypothyroidism had lower work ability than the general population and experienced work limitations due to emotional difficulties and attributed the thyroid disease. These limitations were also most pronounced within the first year of diagnosis. To my knowledge, no other study has examined the risk of labor market exclusion in people with hypothyroidism and only one previous study reported the impact of hypothyroidism on work role functioning (Bianchi, 2004). The qualitative study found that 'feeling drained' was an essential part of feeling hypothyroidism. Like the illness experiences of people with hyperthyroidism, 'feeling drained' was experienced as diffuse and hidden and subjects found it difficult to convert these signs of illness into legitimate claims of absenteeism, despite the experienced impact on daily role function.

These findings were similar to the findings of people with Graves' disease. Therefore the same discussion applies to people with autoimmune hypothyroidism (section 3.2.2.). Lack of statistical power to predict rare outcomes as well as difficulties claiming social welfare because of lack of recognition of diffuse and hidden disabilities may explain the results.

4.2.4. Discussion of the main findings of non-toxic goiter

Study 1 showed that people with non-toxic goiter had a higher risk of unemployment after a year of diagnosis. However, in study 3, people with non-toxic goiter had a higher self-reported work ability compared with the general population on the items on work ability with respect to mental and physical demands. As discussed previously, these work ability items may be prone to a response

bias for persons with thyroid diseases. No study has previously examined the risk of negative labor market outcomes. The symptomatology of non-toxic goiter does not involve specific limitations to the physical or mental work demands. The mixed results for this group do not have an obvious explanation.

4.2.5. Discussion of the main findings of 'other thyroid diseases'

Study 1 did not show any increased long-term risk of having 'other thyroid diseases' (e.g., subacute hypothyroidism and post-partum thyroiditis), whereas study 3 reported lower global work ability than the general population. Yet no impact was observed on the work ability compared to non-toxic goiter. Because this diagnostic group consisted of a variety of thyroid diseases the sample size in the survey was small and was not shown consistently on other items or across methods, no reliable conclusions can be drawn from this diagnostic sub-group.

4.3. Methodological considerations, strengths and weaknesses

4.3.1. Use of register data

Although DREAM has been considered more reliable than self-reported data on sickness absence (Hjollund N.H. et al. 2007), some of the known limitations of the DREAM register are not accounted for. Social reimbursements are only registered in DREAM if the municipality has made a social transfer payment. Thus, those people who are on self-financed sickness leave or unemployment were not registered. Although most people in Denmark are financially covered by the social reimbursements registered in DREAM (Burr et al. 2011), it is not an exhaustive measure. Neither was this study exhaustive of all the outcomes of relevance to labor market exclusion, e.g., early retirement by voluntary early retirement (Danish: Efterløn).

4.3.2. Assessment of clinical information

Clinical data on thyroid disease was restricted to study entrance and did not account for clinical changes in diagnostic sub-groups over time, e.g., having permanent hypothyroidism after the treatment of Graves' disease. However, this study accounted extensively for co-morbidity throughout the entire study period, which can be an important aspect of having a thyroid disease (Brandt et al. 2013b; Brandt et al. 2013c; Thomsen et al. 2005; Thvilum et al. 2013a; Thvilum et al. 2014). In planning the study, standard measures of comorbidity, such as the Charlson index

(Charlson et al. 1987) or the Elixhauser comorbidity measure (Elixhauser et al. 1998), were considered. However, the diseases in these indexes are selected and scored to optimize the prediction of mortality. For this reason, they do not include many chronic diseases with a potentially great impact on disability. Therefore, a larger set of chronic diseases were controlled for during the entire follow-up period, including 32 somatic and 7 psychiatric disorders classified within the 22 domains of ICD-10

4.3.3. Statistical methods

Among the major strengths of the study was the use of a multi-state model allowing for simultaneous analyses of changes between states. Competing risks are a problem when applying multiple outcomes in survival analysis because the occurrence of one event might prevent the occurrence of another (Lau et al. 2009). By applying a multi-state model in this study, the problem of competing risks is avoided (Andersen 2002a). The prospective design enabled investigation of long-term risks in a wide range of thyroid diseases, which also allowed controlling for a wide range of important confounders over time. The estimates of the different exposures in the model all seemed to follow a plausible pattern across measurements within the different diagnostic subgroup, so that elevated risks of, e.g., sickness absence, also led to a decreased chance of returning to work.

4.3.4. Use of qualitative research methods

No previous study has, to my knowledge, been published exploring the illness experience of people with thyroid diseases within a qualitative research methodology. Because of its analytical nature, one of the great strengths of the qualitative research methodology is its potential to illuminate dynamic aspects of subjective experience that are often limited in quantitative research designs. However, in qualitative methods the quality of such data is often a result of how the data is gathered. One-to-one interviews were chosen to facilitate the identification of relevant meanings in a flexible and collaborative process (Rapley 2001). The interviews were semi-structured in the sense that the participants were asked open questions on the same predefined themes. One of the main strengths of the study was the rich data that were able to illustrate the relevance of the major themes and thus applied across participants.

4.3.5. Generalizability of study results

This sample was recruited from two Danish out-patient clinics and may not represent a clinical population treated in general practice. Although they represent two different regions of Denmark, people recruited from a hospital setting may have been more impacted by their disease. Patients with hypothyroidism are mainly treated in primary care, and thus, the limitations of generalizability might particularly apply within this subgroup. Also, the Danish labor market has been described as a flexicurity model, securing easy access to the social security system, but also confers little formal employment protection allowing, for instance, an employer to lay off an employee with long-term sickness absence. Therefore, these results may be difficult to transfer to other countries with other social security systems.

4.4. Future perspectives

In this Ph.D. project, a theoretical and empirical distinction between work ability and labor market exclusion was made and adapted to the conceptual framework of the ICF model. However, future studies need to clarify the role of individual and contextual factors in the development of thyroid associated work disability as these remain poorly understood. In doing so, factors that help retain the link to employment, regardless of an impaired capacity to work, could be identified.

Modern work life poses high demands on mental abilities and productivity (Brun & Milczarek 2007), and since thyroid diseases also affect psychological functions the psychological aspects of work ability may be particularly relevant in autoimmune thyroid diseases. In the questionnaire study, data was collected to assess the effect of psychosocial work environment on work ability and labor market exclusion. However, these analyses were beyond the aims of the present Ph.D. project as they await an appropriate follow-up period. The identification of work environment factors can play an important role in prevention strategies, as it is possible to intervene against adverse environmental factors and reinforce positive factors in the working environment.

This project compared thyroid diseases with the general population. The findings from the qualitative study suggested that the diffuse and hidden nature of the work disability experienced by people with hyper- and hypothyroidism might not be specific to people with thyroid diseases. Comparing work disability in specific subtypes of thyroid diseases with other medical conditions e.g., chronic pain, diabetes or chronic fatigue syndrome, might help identify general factors that can help prevent consequences of a decreased capacity to work. Comparing thyroid diseases with these medical conditions might also clarify whether people with thyroid diseases can benefit from general psychosocial interventions that help manage symptoms at work and everyday life. The specific needs for interventions among people with thyroid diseases could be assessed from the data gathered in the 2012/2013 thyPROw survey.

These future research perspectives could help identify important factors that might prevent labor market exclusion as well as identify rehabilitation strategies that might help people with thyroid diseases to regain the link to employment.

4.5. Practical implications

There has been an assumption that thyroid diseases alone do not cause work disability (Reed 2005b). However, the findings of the project showed that people with thyroid diseases do experience work disability- either as work limitations while at work or as difficulties retaining the link to employment. Although the risk of work disability can vary according to diagnosis and disease duration, these findings suggest that professionals that encounter individuals with thyroid diseases can play an important role in acknowledging work disability as a valid consequences of thyroid diseases.

It is also important that professionals are aware that risks of labor market exclusion are most pronounced in the first year with the disease. Although these risks diminish with time, they can nevertheless remain elevated. In particular people with Graves' orbitopathy might benefit from strategies that prevent unnecessary labor market exclusion. People with non-toxic goiter may be at particular risk of unemployment after a year with the diagnosis. Also, it cannot be ruled out that temporary or permanent work disabilities can occur in people with toxic nodular goiter, autoimmune hypothyroidism and Graves' hyperthyroidism after a year with diagnosis.

Because of the diffuse, hidden and subjective nature of the disability experienced by people with autoimmune hyperthyroidism and Graves' hyperthyroidism without orbitopathy the need for rehabilitation may be difficult to identify and treat within the traditional biomedical setting.

Self-reported outcomes can be an important clinical tool that can help supplement the clinical assessment of thyroid associated work disability and identify the need for rehabilitation. Generic items on work ability (role physical and role emotional scales of SF-36) remain useful for people not currently working at the time of completion of a questionnaire.

4.6. Conclusion

Thyroid diseases can cause work disability. Patients with thyroid diseases have a higher risk of temporary and permanent labor market exclusion and a lower self-reported work ability compared with the general population. The risks of labor market exclusion are influenced by the type of diagnosis and the duration of disease. People with Graves' orbitopathy have the highest risk of

temporary and permanent exclusion from the labor market within the first year of diagnosis and in subsequent years.

The illness experience of autoimmune hypo- and hyperthyroidism plays an important role in the management of thyroid associated disability. The signs of illness are difficult to conceptualize as medical signs of disease and are difficult to validate medically. Therefore, self-reported health-related quality of life outcomes can be an important clinical supplement to assess thyroid associated work ability. The development and evaluation of different work ability items shows that a work ability scale (ThyPROw) assessing thyroid associated work disability presents good predictive validity. Generic items on work ability (role physical and role emotional scales of SF-36) remain useful for people not currently working at the time of completion of a questionnaire and are useful for general population comparison.

Subjects with thyroid diseases report lower work ability than the general population. Compared with those with non-toxic goiter, people with Graves' disease and autoimmune hypothyroidism reported more thyroid associated work limitations along with limitations due to emotional difficulties and/or physical health. Lower work ability is more likely to be reported within the first year of diagnosis. Self-reported thyroid associated work disability is associated with subsequent exclusion from the labor market.

Comparing the results across methods showed that the ICF model could be used as a theoretical framework in explaining work disability in thyroid diseases. Further insights into the mechanisms causing work disability in person with thyroid disease would be a register follow-up of the 2012 survey, which could identify potential contextual factors (e.g., work environment) as well as individual factors (e.g., disease severity, need for psychosocial interventions), which could make an important difference in prevention and rehabilitation strategies.

5. English summary

Thyroid diseases are chronic diseases that are prevalent in the general population. Many of the diseases cause a complex range of physical and psychological symptoms and decrease quality of life. Although work ability is an important aspect of quality of life, few studies have examined the impact of work role function on thyroid disease and the possible related mechanisms are poorly understood. The conceptual framework of World Health Organization's: International Classification of Functioning (ICF) was used to explain how thyroid diseases can cause work disability. Thyroid associated limitations in the ability to perform activities at work (work ability) can subsequently lead to difficulties in maintaining employment (sickness absence, unemployment, disability pension). The overall aim of this thesis was to evaluate whether thyroid diseases cause work disability.

This aim was examined in three studies: 1) A register-based cohort study, 2) a qualitative interview study, and 3) a survey. The work ability among people with the following thyroid diseases was examined: Graves' disease with or without orbitopathy, autoimmune hypothyroidisme, non toxic goiter, toxic nodular goiter and 'other thyroid diseases' (e.g., subacute hypothyroidism).

1) The risk of labor market exclusion was examined in a population of thyroid patients recruited from two Danish Hospitals (Odense University Hospital and Copenhagen University hospital (Rigshospitalet). The population with thyroid diseases (n=862) and their matched controls (n=7,641) from a general population sample were observed in Danish national registers of social benefits, health, and work characteristics covering the period 1994 to 2011. The risks of labor market exclusion by sickness absence, unemployment, disability pension or difficulties returning to work in the first year after a thyroid diagnosis and subsequent years was compared with that of the controls. The analyses were adjusted for gender, job type, household status, immigrant status, season and time period, region of living, and co-morbidity. The adjusted hazard ratios (HRs) were estimated in a multistate model through Cox regression analyses.

2) The illness experience of people with thyroid disease was examined in a qualitative study. Sixteen in-depth interviews with medically treated patients were conducted. Participants were purposefully selected according to diagnosis (autoimmune hypothyroidism, Graves' hyperthyroidism with or without orbitopathy) as well as disease duration (>6 months). The

interviews were semi-structured and included open-ended questions about the participants' experienced health, thyroid disease, daily life and work. The transcribed interviews were analyzed and major themes identified by Interpretative Phenomenological Analysis.

3) The work ability of people with thyroid disease was examined in a survey in which a work ability scale of people with thyroid diseases was developed and evaluated. The construct validity of 16 work ability items was evaluated through confirmatory factor analysis and tests of differential item functioning. The work ability among 507 employed thyroid patients was compared with a general population sample (n=15,050) using ordinal logistic regression. Five work ability scales was compared in analyses of thyroid diagnostic subgroups using linear regression. A longitudinal logistic regression analysis examined whether self-reported thyroid-specific work ability predicted early retirement over four years.

The results from the three different studies showed that thyroid diseases can cause work disability. The register-based study showed that in the first year after diagnosis, patients with thyroid diseases had an increased risk of sickness absence, lower rate of return to work from sickness absence, and a higher risk of disability pensioning. In subsequent years, the risk of sickness absence diminished but remained slightly higher than in the general population and the rate of return to work remained low. The risk of unemployment was higher than in the general population, but the risk of disability pension attenuated. The type and extent of disability differed according to diagnostic categories and disease duration. Patients with Graves' orbitopathy had the highest risk of temporary and permanent labor market exclusion among the diagnostic sub-groups. These risks were most pronounced within the first year of diagnosis, but remained elevated in subsequent years. The risks of labor market exclusion for people with autoimmune hypothyroidism, Graves' hyperthyroidism and toxic nodular goiter were only significant within the first year of diagnosis. Non-toxic goiter was associated with increased risk of unemployment.

The results from the qualitative study showed that the way autoimmune hypothyroidism and Graves' hyperthyroidism with or without orbitopathy are experienced influences the way disabilities are conceptualized and managed at work. Signs of hyper- and hypothyroidism were related to difficulties in meeting the daily work demands. These signs were experienced as diffuse and hidden and difficult to legitimize as valid causes of sickness absence. The work limitations

were often kept a secret at the work place, because the participants feared other people's reaction to the disabilities. Because thyroid associated disability was often experienced in the absence of medically observable signs (e.g., clinical blood tests), these results suggest that patient-reported outcomes can be an important clinical tool to assess the psychosocial aspects of work disability in thyroid patients.

The development and evaluation of different work ability items showed that a work ability scale (ThyPROw) assessing thyroid associated work disability had good predictive validity. Generic items on work ability (role physical and role emotional scales of SF-36) remain useful for people not currently working at the time of completion of a questionnaire and for general population comparison.

The results from the survey also showed that people with thyroid diseases reported lower work ability than people from the general population. Work disability in thyroid diseases predicted labor market exclusion within the next four years. People with autoimmune hypo- and hyperthyroidism experienced lower work ability than the general population and report more thyroid-specific limitations along with more work role limitations due to emotional and/or physical difficulties. These results were most pronounced in the first year.

In conclusion, the results showed that thyroid diseases can cause work disability – either as a decreased capacity to work, and/or as difficulties retaining the link to the labor market. Work ability items in self-reported quality of life questionnaires can be an important supplementary clinical tool to identify rehabilitation needs. Future studies should clarify factors that can improve and worsen the capacity to work and thus identify important factors that help individuals with thyroid diseases to maintain the link to employment.

6. Danish summary (dansk resumé)

Thyreoidea sygdomme betegner en række sygdomme med relation til skjoldbruskkirtlen (thyreoidea). De er forbundet med enten en forstørrelse af skjoldbruskkirtlen (struma) eller med en ændret thyreoida funktion, der medfører for højt eller for lavt stofskifte. Sygdommene er udbredte i den generelle befolkning og har ofte et kronisk forløb. De sygdomme, der medfører ændret funktion af skjoldbruskkirtlen, medfører et bredt spektrum af både fysiske og psykiske symptomer og kan give nedsat livskvalitet. Evnen til at arbejde er et vigtigt aspekt af livskvaliteten. Ikke desto mindre er der få studier, som har undersøgt, hvorvidt arbejdsevnen er nedsat blandt personer med thyreoidea sygdomme, og de mulige mekanismer mellem sygdommen og arbejdsevnen er dårligt belyst.

World Health Organizations model: 'International Classification of Functioning (ICF) bruges i denne afhandling til at forklare, hvordan thyreoidea sygdomme kan påvirke arbejdsevnen og fastholdelsen på arbejdsmarkedet. Thyreoidea relaterede begrænsninger i evnen til at arbejde (arbejdsevne) kan medføre vanskeligheder med at fastholde beskæftigelse (sygefravær, arbejdsløshed, og førtidspension). Formålet med denne afhandling var at evaluere, hvorledes thyreoidea sygdomme påvirker arbejdsfunktionen og evnen til at fastholde arbejde.

Dette formål blev undersøgt i tre studier: 1) En registerbaseret kohorte undersøgelse, 2) en kvalitativ interviewundersøgelse og 3) en spørgeskemaundersøgelse. De thyreoideasygdomme, der blev inkluderet i denne afhandling, var: atoksisk struma, toksisk nodulær struma, autoimmun hypothyroidisme, Graves' sygdom med eller uden orbitopati og en gruppe med andre thyreoidea sygdomme (fx subakut hypothyreoidisme).

1) I registerstudiet blev risici for eksklusion fra arbejdsmarkedet undersøgt longitudinelt. En population af ambulante patienter med thyreoidea sygdomme (n=862) og en population af matchede kontrolpersoner fra den generelle befolkning (n=7,641) blev observeret i danske nationale registre. Fra disse registre blev der hentet oplysninger om deltagernes helbred, sociale ydelser og arbejdsforhold i perioden 1994 til 2011. Risici for eksklusion fra arbejdsmarkedet (sygefravær, ledighed, førtidspension) eller vanskeligheder ved at vende tilbage til arbejdet blev estimeret i en multistate model ved hjælp af Cox regression analyser. Hazard Ratios (HRs) blev estimeret i det første år med thyreoidea sygdomme og i de resterende år sammenlignet med kontrolpopulation. Der

blev lavet separate analyser for alle thyreoidea sygdommene og på tværs af diagnoser. Analyserne blev justeret for køn, alder, jobtype, husstandsstatus, immigrantstatus, sæson og tidsperiode, region og komorbiditet.

2) Selve sygdomsoplevelsen hos folk med thyreoidea sygdomme blev undersøgt i et kvalitativt studie, hvor seksten dybdegående interviews blev foretaget. Deltagerne blev udvalgt i henhold til deres diagnose (autoimmun hypothyreoidisme, Graves' sygdom med eller uden orbitopati) og til sygdomslængde (>6 måneder). Interviewene var semi-strukturerede, men med åbne spørgsmål, der vedrørte deltagernes oplevede thyreoidea sygdom, hverdag og arbejdsliv. De transkriberede interviews blev analyseret i henhold til 'Interpretative Phenomenological Analysis'.

3) Arbejdsevnen hos folk med thyreoidea sygdomme blev undersøgt i en spørgeskemaundersøgelse. Til dette formål blev der udviklet og evalueret en arbejdsevneskala. Konstrukt validiteten af 24 arbejdsevne-items blev evalueret med Confirmatory Factor Analysis (CFA) og Differential Item Functioning (DIF). Arbejdsevnen blandt 507 beskæftigede personer med thyreoidea-sygdomme blev sammenlignet med en population af beskæftigede personer fra den generelle befolkning (n=15050) ved hjælp af ordinal logistik regression. Fem arbejdsevneskalaer blev sammenlignet i analyser af thyreoidea subgrupper ved hjælp af lineær regression. I en longitudinel logistisk regressions analyse blev det undersøgt, hvorvidt thyreoidea-specifik arbejdsevne predikterede tidlig tilbagetrækning med førtidspension i en periode over fire år.

Resultaterne fra de tre forskellige studier viste, at thyreoideasygdomme kan forringe arbejdsevnen og øge risikoen for eksklusion fra arbejdsmarkedet. Det registerbaserede studie viste, at patienter med thyreoideasygdomme havde en forøget risiko for sygefravær, en lavere rate af tilbagevenden til arbejde fra sygefravær og højere risiko for førtidspension i det første år med thyreoideasygdom. I de følgende år blev risikoen for sygefravær mindre, men den var stadig højere end i den generelle befolkning, og det forblev også vanskeligt at vende tilbage til arbejde efter sygefravær eller ledighed. Risikoen for at blive førtidspensioneret forsvandt efter et år med sygdommen, mens risikoen for arbejdsløshed var højere end i den generelle befolkning efter et år med sygdommen. Typen og graden af arbejdsevnen og fastholdelsen varierede alt efter de diagnostiske kategorier og hvor lang tid deltagerne havde haft sygdommen. Patienter med Graves' orbitopati havde den største risiko for midlertidig og permanent eksklusion fra arbejdsmarkedet i de diagnostiske

subgruppeanalyser. Disse risici var mest udtalte i det første år med sygdommen, men forblev forhøjede i de efterfølgende år.

Resultaterne fra det kvalitative studie viste, at måden autoimmun hypothyroidisme og Graves' sygdom med eller uden orbitopati opleves på, har betydning for, hvordan arbejdsevnen bliver manifesteret og håndteret på arbejde. Tegn på hyper- og hypothyroidisme blev relateret til vanskeligheder med at imødekomme kravene i det daglige arbejde. Da tegnene blev oplevet som skjulte og diffuse, var de svære at legitimere som grunde til sygefravær. Mange af deltagerne frygtede omgivelsernes manglende forståelse og skjulte vanskelighederne for andre på arbejdspladsen. Fordi nedsat arbejdsevne ofte ikke blev fulgt af påviselige medicinske tegn (fx kliniske blodprøver) kan selv-rapporterede livskvalitets spørgeskemaer ('patient reported outcomes') være et supplerende klinisk redskab, til at belyse de psykosociale aspekter af den nedsatte arbejdsevne og identificere behov for rehabilitering.

Udviklingen og evalueringen af forskellige arbejdsevne items viste, at en arbejdsevneskala (thyPROw), der målte thyreoidea associeret arbejdsevne, havde en god prediktiv validitet. Generelle items, der måler arbejdsevne (SF-36 fysisk og emotionel rolle funktion), er anvendelige til at vurdere arbejdsevnen hos personer med thyreoidea sygdomme, der ikke er i arbejde på det tidspunkt, spørgeskemaet udfyldes og til at sammenligne med andre populationer.

Personer med thyreoideasygdomme rapporterede lavere arbejdsevne sammenlignet med personer fra den generelle befolkning. Nedsat arbejdsevne i thyreoideasygdomme predikterede også eksklusion fra arbejdsmarkedet i en periode på fire år. Personer med Graves' sygdom og autoimmun hypothyroidisme rapporterede lavere arbejdsevne end den generelle befolkning. De rapporterede også flere thyreoidea-associerede begrænsningerne i arbejdsevnen og flere begrænsninger i rollefunktion på grund af emotionelle og fysiske begrænsninger end folk med atoksisk struma. Disse resultater var mest udtalte indenfor det første år med sygdommen. Primært på grund af begrænset statistisk styrke var der ikke altid overensstemmelse imellem selv-rapporteret arbejdsevne og eksklusion fra arbejdsmarkedet, når resultaterne blev evalueret på tværs af diagnostiske subgrupper.

Resultaterne fra de tre studier viser, at thyreoideasygdomme kan forringe arbejdsevnen – enten i form af nedsat arbejdsfunktion eller i form af vanskeligheder med at fastholde forbindelsen til arbejdsmarkedet. Arbejdsevne items i livskvalitetsspørgeskemaer kan være et supplerende klinisk redskab, der kan identificere behov for rehabilitering. Fremtidige studier bør afklare, hvilke faktorer der kan beskytte og forværre arbejdsevnen, og dermed identificere vigtige faktorer, der kan hjælpe personer med thyreoideasygdomme til at fastholde forbindelsen til arbejdsmarkedet.

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